

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE PROCTER & GAMBLE COMPANY,

Plaintiff,

V.

TEVA PHARMACEUTICALS USA, INC.,

Defendant.

Civil Action No. 04-940-JJF

**PLAINTIFF THE PROCTER & GAMBLE COMPANY'S
POST-TRIAL BRIEF AND PROPOSED CONCLUSIONS OF LAW**

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I. INTRODUCTION

This case arises out of Teva Pharmaceuticals USA, Inc.'s ("Teva") desire to sell generic risedronate despite the existence of The Procter & Gamble Company's ("P&G") valid and enforceable U.S. Patent No. 5,583,122 (the "'122 patent") covering the highly successful and beneficial drug, Actonel.¹ Teva concedes infringement of the asserted claims of the '122 patent, and did so long before trial. Indeed, its sole defense at trial was that the '122 patent is invalid for obviousness and obviousness-type double patenting in view of United States Patent No. 4,761,406 (the "'406 patent"). To prove invalidity on these grounds, Teva had a heavy burden of proof—one of clear and convincing evidence—a burden it did not and could not carry.

At trial, Teva presented only one witness in support of its attack on the validity of the '122 patent. However, that witness, an ostensible technical expert, was not qualified to offer an opinion on obviousness in this case. Even if he were qualified, his opinions do not constitute clear and convincing evidence of obviousness, especially when the Court considers the overwhelming evidence of nonobviousness presented at trial by P&G. In particular, P&G demonstrated that the '406 patent—the sole prior art reference Teva asserts as invalidating—does not render the asserted claims of the '122 patent obvious for several reasons:

First, the '406 patent is not prior art to the '122 patent.

Second, the two-dimensional structural similarity between the formulas for 2-(2-pyridyl)-1-hydroxyethane-1,1-bisphosphonate ("2-pyr EHDP") and risedronate does not render the risedronate compound obvious.

Third, it would not have been obvious to one of ordinary skill in the art to modify the compounds disclosed in the '406 patent to make a new and useful compound to treat osteoporosis, because the '406 patent "teaches away" from the use of pyridyl ethane hydroxy bisphosphonates ("pyr-EHDPs").

¹ Actonel is the trade name for risedronate, a chemical compound having the structure -(3-pyridyl)-1-hydroxyethane-1,1-bisphosphonate ("3-pyr EHDP").

Fourth, given the state of the art in the mid-1980s, a person of ordinary skill would have had no reasonable expectation that risedronate would succeed as a useful treatment for bone disease.

Fifth, objective indicia, including long-felt, but unmet need, unexpected results and commercial success, support the non-obviousness of the asserted claims of the '122 patent.

Finally, because Teva failed to prove obviousness under 35 U.S.C. § 103 by clear and convincing evidence, it also failed to prove that the '122 patent is invalid for obviousness-type double patenting.

Therefore, in light of this evidence, and Teva's total failure of proof, the Court should find the '122 patent infringed, nonobvious, and valid, and enter judgment in favor of P&G.

II. THE '406 PATENT IS NOT PRIOR ART TO THE '122 PATENT

Obviousness is to be determined "at the time the invention was made." 35 U.S.C. § 103; *Graham v. John Deere Co.*, 383 U.S. 1, 14-15 (1966). Pertinent prior art, therefore, only includes those references with effective dates prior to the date of the invention. *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1453 (Fed. Cir. 1984). "In explaining the concept of priority under Section 102(g), the Federal Circuit has explained that '[p]riority goes to the first party to reduce an invention to practice unless the other party can show it was the first to conceive the invention and that it exercised reasonable diligence in later reducing that invention to practice.'" *LifeScan, Inc. v. Home Diagnostics, Inc.*, 103 F. Supp. 2d 345, 367 (D. Del. 2000) (quoting *Price v. Symsek*, 988 F.2d 1187, 1190 (Fed. Cir. 1993)). Priority therefore involves two components: (1) conception and (2) reduction to practice. *Id.*

As discussed in detail below, under the applicable legal standards, Dr. Benedict conceived of risedronate no later than May 3, 1985, more than a month before the filing of the '406 patent. In addition, Dr. Benedict exercised reasonable diligence from his conception of risedronate until he (1) actually reduced to practice the invention under claims 4, 16, and 23 of the '122 patent no later than October 4, 1985, or (2) constructively reduced to practice the

invention under these claims with the filing of the '122 patent application on December 6, 1985. The '406 patent is therefore not prior art to the '122 patent.

A. Risedronate was Conceived Prior to the Filing of the '406 Patent Application

1. Conception of Chemical Compounds

Conception of a chemical compound requires the structure of the chemical compound, and possession of an operative method of making it. *Oka v. Youssefyeh*, 849 F.2d 581, 583 (Fed. Cir. 1988). "Conception [of a chemical compound] does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it." *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991).

2. Corroboration of Conception

Although courts require corroboration of an inventor's testimony as to conception, *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994), they apply a rule of reason to the corroboration requirement. *Woodland Trust v. Flowertree Nursery, Inc.*, 148 F.3d 1368, 1371 (Fed. Cir. 1998) (enumerating factors for rule of reason analysis); *Price*, 988 F.2d at 1195. Under this standard, courts have found that unwitnessed, contemporaneous lab notebooks provide sufficient corroboration. See *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1169-70 (Fed. Cir. 2006); *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1577-78 (Fed. Cir. 1996). Such physical evidence provided in support of oral testimony does not require corroboration because "[t]he trier of fact can conclude what the documents show." *Brown v. Barbacid*, 276 F.3d 1327, 1335 (Fed. Cir. 2002) (quoting *Mahurkar*, 79 F.3d at 1577-78).

3. Conception of Risedronate

After exploring many avenues of potential compounds for treatment of osteoporosis over years of research from the mid-1970s into the early-1980s, in late 1983, Dr. Benedict eventually embarked upon study of pyridyl-containing bisphosphonates. After testing many such bisphosphonates under a research proposal that he and his colleague, Dr. Christopher Perkins, submitted to their supervisor, Dr. Benedict ultimately conceived of the invention claimed in the '122 patent – risedronate – no later than May 3, 1985 when he synthesized the compound for the first time and recorded the synthesis in his laboratory notebook. (P&G's Proposed Findings of Fact ("PFF") ¶ 274; Tr. at 420:19-421:1, 467:5-22 (Benedict Dir.); PTX 67 at PG 53521-53522). Dr. Benedict's lab notebook entry includes the chemical structure for risedronate as well as the chemical reactions utilized to synthesize risedronate, thus demonstrating the chemical composition's preparation. (*Id.*). Dr. Benedict's lab notebook entry is signed and dated. (*Id.*). As a contemporaneous disclosure in a "clearly perceptible form," Dr. Benedict's lab notebook provides the requisite corroborative evidence for his oral testimony at trial as to his conception of risedronate. *Price*, 988 F.2d at 1194; *Burroughs Wellcome*, 40 F.3d at 1228. (PFF ¶ 277; Tr. at 468:8-11, 469:16-20 (Benedict Dir.); PTX 67 at PG 53522). This conception is further corroborated by the fact that risedronate was sent to the University of Arizona for testing on June 3, 1985, three days before the filing of the '406 patent application. The evidence of Dr. Benedict's conception of risedronate is unequivocal. Moreover, Teva offered no evidence whatsoever to rebut this conception date.

B. P&G Exercised Reasonable Diligence in Reducing Risedronate to Practice

1. Reduction to Practice of Pharmaceutical Compounds

"An actual reduction to practice occurs when the inventor (1) constructs a product or performs a process that is within the scope of the claimed invention; and (2) demonstrates that

the invention actually worked for its intended purpose.” *LifeScan*, 103 F. Supp. 2d at 367; *Cooper v. Goldfarb*, 154 F.3d 1321, 1327 (Fed. Cir. 1998); *Estee Lauder Inc. v. L’Oreal S.A.*, 129 F.3d 588, 593 (Fed.Cir.1997). “[R]eduction to practice requires that the invention be sufficiently tested to demonstrate that it will work for its intended purpose.” *Kimberly-Clark*, 745 F.2d at 1445.

If a patent’s claims to a pharmaceutical compound contain no limitation relating to intended use or to discovered properties, “practical utility may be shown by adequate evidence of any pharmaceutical activity.” *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564 (Fed. Cir. 1996). Testing is often required to determine whether a pharmaceutical compound has pharmacological activity. *Fujikawa*, 93 F.3d at 1564. For test results to satisfy the practical utility requirement, “there must be a sufficient correlation between the tests and an asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior.” *Id.* However, the “test results need not absolutely prove that the compound is pharmacologically active.” *Id.* “[T]he mere **identification** of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an ‘immediate benefit to the public’ and thus satisfies the utility requirement.” Manual of Patent Examining Procedure (“MPEP”) § 2107.01 at 2100-25 (emphasis in original). Data from human clinical trials are not required to show utility. MPEP § 2107.03 at 2100-35. Moreover, “proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility.” *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995).

Regardless of when an actual reduction to practice of an invention has been achieved, the filing of a patent application that describes and enables the claimed invention is a

“constructive reduction to practice of the invention.” *Chen v. Bouchard*, 347 F.3d 1299, 1306 (Fed. Cir. 2003); *Hazeltine Corp. v. United States*, 820 F.2d 1190, 1196 (Fed. Cir. 1987).

2. *Corroboration of Reduction Practice*

As with conception, corroboration of an inventor’s testimony is required to establish actual reduction to practice. *Medichem*, 437 F.3d at 1169. Unlike inventors’ oral testimony, the condition of “corroboration” is not imposed on a lab notebook or other documentary or physical evidence as a condition to that item serving as evidence of reduction to practice. *Medichem*, 437 F.3d at 1169-70; *Mahurkar*, 79 F.3d at 1577-78. Although an unwitnessed notebook is not sufficient standing alone to support a claim of reduction to practice, “a notebook, unlike the oral testimony of an inventor, may be weighed, for whatever it is worth, in the final determination of reduction to practice.” *Medichem*, 437 F.3d at 1169-70; *Hahn v. Wong*, 892 F.2d 1028, 1033 (Fed. Cir. 1989); *Reese v. Hurst*, 661 F.2d 1222, 1232 (C.C.P.A. 1981). “Independent corroboration may consist of testimony of a witness, other than the inventor, to the actual reduction to practice or it may consist of evidence of surrounding facts and circumstances independent of information received from the inventor.” *Reese*, 661 F.2d at 1225. “The law does not impose an impossible standard of ‘independence’ on corroborative evidence by requiring that every point of a reduction to practice be corroborated by evidence having a source totally independent of the inventor.” *Cooper*, 154 F.3d at 1330.

3. *Diligence*

In light of the statutory presumption of patent validity under 35 U.S.C. § 282, when a patented invention is conceived prior to the filing date of a reference asserted as prior art, but reduced to practice after the filing date of that reference, the party challenging the validity of the patent must prove by clear and convincing evidence that the alleged prior art patent was filed before the effective invention date for the challenged patent. *Mahurkar*, 79 F.3d at

1578; *see also Loral Fairchild Corp. v. Matsushita Elec. Indus. Co.*, 266 F.3d 1358, 1362-63 (Fed. Cir. 2001). That is, the challenger of the patent's validity must prove by clear and convincing evidence that the inventor did not proceed with reasonable diligence from a time just before the filing of the reference patent until the challenged invention had been reduced to practice. *Mahurkar*, 79 F.3d at 1578.

To demonstrate reasonable diligence, it is not necessary for a party alleging prior invention to have dropped all other work and concentrated solely on the particular invention involved. *Rines v. Morgan*, 250 F.2d 365, 369 (C.C.P.A. 1957); *Izumi Prods. Co. v. Koninklijke Philips Elecs. N.V.*, 315 F. Supp. 2d 589, 608 (D. Del. 2004) (following *Rines*). There also need not be evidence of activity on every single day if a satisfactory explanation is evidenced. *Monsanto Co. v. Mycogen Plant Sci., Inc.*, 261 F.3d 1356, 1369 (Fed. Cir. 2002); *Izumi Prods.*, 315 F. Supp. 2d at 608. Additionally, determining whether the required "reasonable diligence" has been satisfied involves specific inquiry. *Monsanto*, 261 F.3d at 1369; *Izumi Prods.*, 315 F. Supp. 2d at 608.

4. Dr. Benedict was Reasonably Diligent in Reducing Claims 4, 16, and 23 to Practice

To prove that the '406 patent is prior art to the '122 patent, Teva thus bears the burden of proving by clear and convincing evidence that Dr. Benedict was not reasonably diligent in reducing the claimed invention to practice from a time just before the '406 patent was filed on June 6, 1985 until the claims were actually or constructively reduced to practice. *Mahurkar*, 79 F.3d at 1578; *Loral Fairchild*, 266 F.3d at 1361.

After conceiving risedronate on May 3, 1985, Dr. Benedict recrystallized the compound for purification on May 8, 1985 and titrated the compound for purity on May 31, 1985. (PFF ¶ 276; Tr. at 468:15-469:15 (Benedict Dir.); PTX 70 at PG 54042-54043). To

prove that risedronate would inhibit bone resorption and show potential for efficacy in treatment of abnormal calcium and phosphate metabolism, the compound was sent for TPTX testing at the University of Arizona on June 3, 1985. (PFF ¶ 277; Tr. at 468:8-11, 469:16-20 (Benedict Dir.); PTX 67 at PG 53522). The TPTX results from the University of Arizona showed that risedronate inhibited bone resorption in test animals in which an abnormal calcium and phosphate metabolism was induced by artificially controlling a hormone involved in bone metabolism. (PFF ¶ 308; Tr. at 725:5-20 (McOske Dir.); Tr. at 749:20-750:5 (McOske Cross)). Dr. Benedict's testimony regarding the test results is corroborated by the testing results from the University of Arizona.

After receiving efficacy testing data back from the Arizona lab on July 1, 1985, Dr. Benedict continued to be diligent in pursuing these claims through reduction to practice during a time in which he was working contemporaneously with many other compounds, some of which had been synthesized even before risedronate and many of which were part of the invention of the '122 patent. (PFF ¶¶ 278-82; Tr. at 471:12-472:11, 472:24-474:6, 480:15-481:18 (Benedict Dir.); PTX 67; PTX 137; PTX 138). In a biweekly report for the period ending July 26, 1985, Dr. Benedict described how he and his lab were working on synthesizing additional 2, 3, and 4-pyr EHDP. (PFF ¶ 279; Tr. at 471:18-472:23 (Benedict Dir.); PTX 137). Similarly, a biweekly report from Annette Salvagno in Dr. Benedict's lab for the period ending August 9, 1985 shows continued synthesis. (PFF ¶ 279; Tr. at 471:18-472:23 (Benedict Dir.); PTX 138). From September 11-25, 1985, Ms. McOske conducted further TPTX efficacy testing on risedronate, confirming that risedronate inhibits bone resorption and determining that the compound had an even higher potency than that demonstrated by the initial testing in Arizona. (PFF ¶ 310; Tr. 722:12-723:5 (McOske

Direct); Tr. 443:4-14 (Benedict Direct)). These testing efforts support Dr. Benedict's continued diligence.

In a further showing of substantial diligence, from October 2-4, 1985, toxicity testing was actually conducted on risedronate, revealing that, in addition to its antiresorptive potency, the compound would likely be safe for use in the treatment of abnormal calcium and phosphate metabolism. (PFF ¶¶ 353-59; Tr. at 476:21-477:11 (Benedict Dir.); Tr. at 775:17-776:21, 777:2-779:17, 788:13-17, 779:18-780:10, 783:16-22 (Eastman Dir.); Tr. at 865:6-866:14 (Miller Dir.); PTX 82). The toxicity data from this study, in combination with the efficacy data already obtained, supported the belief that would likely be an effective and safe treatment for abnormal calcium and phosphate metabolism. Following the toxicity studies on risedronate, similar studies were conducted on 2-pyr EHDP from October 30, 1985 to November 1, 1985 and on 4-pyr EHDP from December 4-6, 1985, as well as on other compounds that were part of the invention of the '122 patent. (PFF ¶¶ 360-70; Tr. 777:13-18, 780:11-783:7, 783:23-785:21, 789:18-792:5 (Eastman Dir.); Tr. at 865:6-867:9 (Miller Dir.); PTX 81; PTX 82; P-36a).

In sum, Dr. Benedict worked diligently from the time risedronate was first synthesized and conceived on May 3, 1985 (prior to the filing of the '406 patent application on June 6, 1985) through December 6, 1985, by which time risedronate was shown to be effective in inhibiting bone resorption; to be safe to administer at effective doses; and consequently to have a very favorable safety margin, or dosage range over which the compound could be safely and effectively administered. The documentation supporting Dr. Benedict's diligent progression toward reduction to practice is robust and supports and corroborates a conception of the inventions claimed in claims 4, 16, and 23 dating back to May 3, 1985. Thus, the

inventions of claims 4, 16, and 23 pre-date the filing of the '406 patent and were diligently reduced to practice thereafter. As a result, the '406 reference is not prior art to any of the asserted claims.

III. EVEN IF THE '406 PATENT WERE PRIOR ART, IT DOES NOT RENDER THE '122 PATENT OBVIOUS UNDER 35 U.S.C. § 103

Teva contends that claims 4, 16 and 23 of the '122 patent would have been obvious to one of ordinary skill in the art in the mid-1980s in light of the '406 patent. To support this contention, Teva offered the testimony of its sole technical expert, Dr. George R. Lenz, a medicinal chemist who, until Teva hired him for this litigation, had no experience with bisphosphonates, their mechanisms of action, or the state of understanding of bisphosphonates in the mid-1980s. (PFF ¶¶ 92-103; Tr. at 153:1-155:13 (Lenz Cross)). Fundamentally, Teva's obviousness argument is premised on the structural similarity of two chemical compounds: 2-pyr EHDP and risedronate. Teva argues that because the 2-pyr EHDP compound disclosed in the '406 patent and risedronate (3-pyr EHDP) are structurally similar positional isomers, and because virtually all known bisphosphonates allegedly show antiresorptive activity, the asserted claims of the '122 patent are obvious. (Tr. at 6, 17 (Teva Opening)).

As a matter of fact and of law, Teva's obviousness contentions fail. First, as detailed above, Teva has failed to prove that the '406 patent is prior art to the '122 patent at all. Moreover, even if the '406 patent is prior art, as set forth in detail below, the evidence at trial does not support Teva's obviousness position. On the contrary, the record unequivocally demonstrates that claims 4, 16 and 23 of the '122 patent are nonobvious and valid.

A. The ‘122 Patent is Presumed Valid, and Teva Must Prove Obviousness by Clear and Convincing Evidence

The ‘122 patent is presumed valid. *See* 35 U.S.C. § 282; *see also Al-Site Corp. v. VSI International Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999). This presumption extends to each independent and dependent claim of the patent, irrespective of the validity of the other claims. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 446-47 (Fed. Cir. 1986). To overcome this presumption, Teva must demonstrate by clear and convincing evidence that the ‘122 patent is invalid. *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1353 (Fed. Cir. 2003); *Forest Labs. v. Ivax Pharm., Inc.*, 438 F. Supp.2d 479, 485 (D. Del. 2006) (accused infringer failed to rebut presumption of validity by “clear and convincing evidence”). “Clear and convincing” evidence is evidence that “proves in the mind of the trier of fact an abiding conviction that the truth of a factual contention is highly probable.” *Intel Corp. v. International Trade Comm’n*, 946 F.2d 821, 830 (Fed. Cir. 1991); *see also Merck & Co. v. Teva Pharms. USA, Inc.*, 228 F. Supp.2d 480, 496 (D. Del. 2002).

B. Teva Failed to Meet its Burden of Proving the ‘122 Patent is Obvious by Clear and Convincing Evidence

Teva has challenged the validity of the ‘122 patent by contending that the asserted claims are obvious under 35 U.S.C. § 103. (*See* Tr. at 6:14-18 (Teva Opening)). Under Section 103, a patented invention may be invalid for obviousness only if the differences between the claimed invention and the prior art “are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art.” Obviousness is a legal determination, which turns on the objective analysis of underlying factual inquiries. *Forest Labs.*, 438 F. Supp.2d at 492. Specifically, the trier of fact must consider four issues: (1) the scope and content of the prior art; (2) the level of

ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness. *Id.* (citing *Graham*, 383 U.S. at 17-18).

Teva has failed to carry its heavy burden of proving obviousness by clear and convincing evidence because, among other reasons:

- Teva's proposed definition of one of ordinary skill in the art, which suggests that *any* chemist with a Ph.D. has the requisite level of skill in the art, is unsupported by the record;
- Teva's sole technical expert, Dr. George R. Lenz, and its only witness to offer affirmative evidence regarding the validity of the '122 patent, *offered no opinion* consistent with an appropriate definition of one of ordinary skill in the art;
- Dr. Lenz does not have the necessary education, experience or expertise in organophosphorus chemistry and, in particular, bisphosphonates to qualify as an expert under Rule 702. As a result, he is not qualified to offer an opinion on what would have been obvious to one of ordinary skill in the art in the mid-1980s; and
- Teva's obviousness contentions are premised on a legally improper hindsight analysis necessitated by Dr. Lenz's total lack of experience with bisphosphonates before being hired by Teva in this case.

Given these deficiencies in proof, Teva has not and cannot demonstrate by clear and convincing evidence that the '122 patent is obvious in view of the prior art. On the contrary, the evidence at trial demonstrates that the asserted claims of the '122 patent are nonobvious and valid.

1. The Level of Ordinary Skill in the Art in the Mid-1980s

The obviousness of a patented invention is determined from the perspective of one of ordinary skill in the art, *In re Gorham*, 933 F.2d 982, 986 (Fed. Cir. 1991), and the law presumes that the hypothetical person of ordinary skill knows all relevant prior art. *See Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985).

The Federal Circuit has identified several factors that may be used in determining the level of ordinary skill in the art, including, *inter alia*, (1) the educational level of the inventor; (2) the types of problems encountered in the art; (3) the prior art solutions to those problems; (4) the rapidity with which innovations are made; (5) the sophistication of the technology; and (6) the educational level of active workers in the field. *See e.g., Envtl. Designs Ltd. v. Union Oil Co. of Calif.*, 713 F.2d 693, 696-97 (Fed. Cir. 1983). “These factors need not be present in every case and certain factors may be more predominate in some cases than in others.” *Forest Labs.*, 438 F. Supp.2d at 488 (citations omitted).

At trial, P&G presented the testimony of Dr. Charles McKenna, an expert in organophosphorus chemistry who devotes approximately 80% of his work to bisphosphonates. (PFF ¶¶ 45, 47; Tr. at 545:7-10; 546:15-18 (McKenna Dir.)). As Dr. McKenna testified, in the mid-1980s, a person of ordinary skill in the art relevant to the ‘122 patent would have had at least a Ph.D. in synthetic or bio-organic chemistry, as well as additional training in phosphorus chemistry, involving either a post-doctoral program or industry experience researching or working with such compounds. (PFF ¶ 212; Tr. at 555:18-24, 558:6-11 (McKenna Dir.)). Teva’s expert, Dr. Lenz, admitted that he had no opinions on whether the asserted claims of the ‘122 patent would have been obvious to a person of ordinary skill in the art as defined by Dr. McKenna. (PFF ¶ 218; Tr. at 199, 200:9-14 (Lenz Cross)).

Not surprisingly, Teva and Dr. Lenz dispute this definition of one of ordinary skill in the art. Instead, Dr. Lenz suggested that one of ordinary skill in the art in the mid-1980s would be a Ph.D. chemist with several years of experience in the pharmaceutical industry and in drug discovery, design and development. (Tr. at 77 (Lenz Dir.)). In addition, when asked

on cross examination about this definition, Dr. Lenz conceded that a person of ordinary skill in the art in the 1980s would have had knowledge of the pharmacology and mechanism of action of bisphosphonates – even though Dr. Lenz admitted that he did not meet this definition because he did not have such knowledge “[b]ack in the middle of the 1980s.” (PFF ¶¶ 216, 220; Tr. at 202:20-24, 203:7-9 (Lenz Cross)).

For several reasons, the record supports P&G’s definition of a person of ordinary skill in the art relevant to the ‘122 patent. As an initial matter, the art relevant to the ‘122 patent relates to “pharmaceutical compositions containing geminal [bis]phosphonates,” (JTX 1, col. 1:1-2), “which are useful in treating or preventing diseases characterized by abnormal calcium and phosphate metabolism, in particular those which are characterized by abnormal bone metabolism.” (JTX 1, col. 1:13-15).

Given this technical field, training and experience with organophosphorus compounds (and in particular bisphosphonates) would be required for ordinary skill in the art because of the unique nature of those compounds. (PFF ¶ 213; Tr. at 556:1-3, 558:21–559:4 (McKenna Dir.)). Specifically, as a class, organophosphorus compounds are unique because they contain the element phosphorus, which distinguishes them from other organic compounds. (PFF ¶ 214; Tr. at 556:1-6 (McKenna Dir.)). In the area of pharmaceuticals, phosphorus plays a particularly significant role in many biomolecules, such as DNA, ADP (the molecule responsible for energy transactions with many enzymes), and bone. (PFF ¶ 214; Tr. at 556:9-17 (McKenna Dir.)). These unique properties have led many esteemed scientists, such as Dr. McKenna, to devote their careers to the study of phosphorus chemistry. (PFF ¶ 215; Tr. at 556:18-557:23 (McKenna Dir.)).

Further, in the mid-1980s, the knowledge and understanding of bisphosphonates presented difficult challenges for scientists as they attempted to develop new and useful compounds for the treatment of diseases characterized by abnormal bone metabolism. (See PFF ¶ 148; Tr. at 371:10-21 (Bilezikian Dir.)). In particular, there was no reliable understanding of the structure-activity relationships of bisphosphonates in the mid-1980s² (PFF ¶ 182; Tr. at 565:11-15 (McKenna Dir.)); no clear and reliable understanding of the factors that would determine the relative activities of bisphosphonates (PFF ¶ 183; Tr. at 565:24-566:5 (McKenna Dir.)); no clear and reliable understanding of which bisphosphonates would be toxic (PFF ¶ 184; Tr. at 566:6-9 (McKenna Dir.)); and no clear understanding of the effect that modifying the structure of a particular bisphosphonate would have on its safety or efficacy. (PFF ¶ 187; Tr. at 566:24-567:5 (McKenna Dir.)). Given this lack of knowledge and understanding of bisphosphonates, as well as the unpredictability of their properties, one of ordinary skill in the art would necessarily need, as Dr. McKenna opined, training, education and experience with organophosphorus compounds in order to understand and work with the technology relevant to the '122 patent. See Fed. R. Evid. 702 (expert witness must have "knowledge, skill, experience, training, or education" in relevant subject area).

Moreover, the definition of one of ordinary skill in the art offered by Teva and Dr. Lenz is inconsistent with the definition adopted by this Court in *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 228 F. Supp. 2d 480 (D. Del. 2002), a case concerning the identical scientific field (the treatment of osteoporosis using bisphosphonates) during the same time period at issue here (the mid-1980s). In *Merck*, this Court evaluated whether the patent claiming alendronate, another bisphosphonate compound used for the treatment of

² The phrase "structure activity relationship" means a formal study of a fairly significant body of compounds that are varied with respect to some activity, typically a biological activity. An attempt is then made to correlate the data such that the activity can be explained by the structure in every case. (See PFF ¶ 181; Tr. at 565:1-10 (McKenna Dir.)).

osteoporosis, was obvious in view of the prior art.³ The Court, in rejecting Teva's proposed definition in that case, held that a person of ordinary skill in the art in 1984 was:

an individual who would have both a professional or graduate degree in either the medical sciences, chemistry, medicinal chemistry, pharmacology, or a related field, and a "knowledge of the pharmacology and/or mechanisms of action of bisphosphonates."

Additionally, a person of ordinary skill in the art would be aware of work being done with bone metabolism, and would have been exposed to lectures and publications dealing with the pharmaceutical chemistry of agents that act on bone or influence metabolism.

Merck, 228 F. Supp.2d at 501 (citations omitted).

Teva has now, for a second time, offered a definition of a person of ordinary skill in the art in the mid-1980s unsupported by and in conflict with the evidence at trial, and its expert, Dr. Lenz, has offered no opinions under an appropriate definition. (PFF ¶ 218; Tr. at 199; 200:9-14 (Lenz Cross)). Accordingly, Teva has failed to present any affirmative evidence, much less clear and convincing evidence, of what one of ordinary skill in the art in the mid-1980s would find obvious.

2. *Dr. Lenz is Not Qualified to Offer Opinions on Persons of Ordinary Skill in the Art in the Mid-1980s*

Despite its heavy burden to prove invalidity by clear and convincing evidence, Dr. Lenz, Teva's sole technical expert, and the only witness during Teva's case-in-chief to provide testimony about "what people skilled in the art would have known" in the mid-1980's, (Tr. at 95:14-17 (Lenz Dir.)), was not qualified to opine on this subject.

To qualify as an expert under Federal Rule of Evidence 702, a witness must first establish his expertise by demonstrating "knowledge, skill, experience, training, or education" in the relevant subject area. Fed. R. Evid. 702. Dr. Lenz does not qualify as an expert in the

³ The patent concerning alendronate was filed in 1984 and issued in 1986. (PFF ¶ 189; Tr. at 228 (Lenz Cross); DTX 42).

subject area relevant to the '122 patent; he lacks knowledge, skill, experience, training and education in the relevant subject area – *i.e.*, organophosphorus compounds, and in particular bisphosphonates, which are useful in treating or preventing diseases characterized by abnormal bone metabolism. (*See, e.g.*, JTX 1, col:1:1-20).

Dr. Lenz has no formal education or training in bisphosphonates, osteoporosis, or the treatment of bone disease. (PFF ¶ 95; Tr. at 168:1-13 (Lenz Cross)). At no time during his entire professional career as a chemist did Dr. Lenz ever work with bisphosphonates. (PFF ¶ 97; Tr. at 170 (Lenz Cross)). He has never made a bisphosphonate or supervised any research concerning bisphosphonates. (PFF ¶ 97; Tr. at 153; 157 (Lenz Cross)). He has never published on either bisphosphonates or osteoporosis, never been asked to make a presentation on organophosphorus compounds, bisphosphonates, or osteoporosis, and holds no patents concerning bisphosphonates, osteoporosis, or the treatment of diseases related to abnormal calcium or phosphate metabolism. (PFF ¶ 99-101; Tr. at 158; 161-62; 165-66 (Lenz Cross)).

In addition to never working with bisphosphonates, Dr. Lenz knew little, if anything about such compounds before being hired by Teva for this case. Dr. Lenz admitted that “[b]ack in the middle of the 1980s [he] did not work in bisphosphonates or phosphorus chemistry.” (PFF ¶ 220; Tr. at 203:7-9 (Lenz Cross)). Before beginning his work in this litigation, Dr. Lenz had absolutely no hands-on experience with any kind of bisphosphonate, including risedronate, (PFF ¶ 97; Tr. at 153-54; 182 (Lenz Cross)), and no specific knowledge of the mechanisms of action of bisphosphonates. (PFF ¶ 103; Tr. at 154 (Lenz Cross)).

Likewise, with respect to the screening assays P&G employed in the mid-1980s to test the efficacy of new bisphosphonate compounds (*i.e.*, the Schenk and TPTX assays), (*see* PFF ¶ 286; Tr. at 715:7-11 (McOske Dir.)), Dr. Lenz had never even heard of (let alone

conducted or supervised) either screening assay before being hired by Teva as an expert witness in this case. (PFF ¶¶ 104-106; Tr. at 176-77, 180-81, 203:7-9 (Lenz Cross)). Dr. Lenz admitted, however, that if he had been one of the people working with bisphosphonates in the 1980s (which he was not), he would have known about the Schenk assay before 2006. (PFF ¶ 106; Tr. at 178 (Lenz Cross)).

In addition, Dr. Lenz has had no experience with the treatment of osteoporosis. (PFF ¶ 98; Tr. at 155 (Lenz Cross)). He has never treated patients with abnormal calcium or phosphate metabolism, and has never worked with medical doctors who were treating bone diseases. (PFF ¶ 98; Tr. at 155 (Lenz Cross)). Dr. Lenz has never supervised any research directed to developing compounds for the treatment of osteoporosis, or any metabolic bone disease for that matter. (PFF ¶ 98; Tr. at 157-58 (Lenz Cross)).

Given Dr. Lenz's total lack of knowledge, skill, experience, training, and education related to either bisphosphonates or the treatment of osteoporosis, he fails to qualify as an expert in the subject matter related to the '122 patent. *See* Fed. R. Evid. 702. As a result, Dr. Lenz cannot opine on the level of ordinary skill in the art, nor can he offer a reliable opinion on whether a person of ordinary skill would find the '122 patent obvious in the mid-1980s. *See, e.g., Lauria v. Nat'l Railroad Passenger Corp.*, 145 F.3d 593, 597 (3rd Cir. 1998) (proffered witness must possess the necessary knowledge, skill, training or education to assist trier of fact). Consequently, Teva has offered no admissible evidence that the '122 patent was obvious in view of the relevant prior art. *See, e.g., Chemipal Ltd. v. Slim-Fast Nutritional Foods Int'l*, 350 F. Supp.2d 582 (D. Del. 2004) (failure to meet burden of proof where expert's testimony unreliable).

3. Dr. Lenz has engaged in improper hindsight analysis

Given Dr. Lenz's lack of experience or knowledge concerning bisphosphonates or the treatment of bone disease during the relevant time period of the mid-1980s, his analysis of the validity of the '122 patent and the asserted prior art is based entirely on impermissible hindsight analysis. "A critical step in analyzing the patentability of claims pursuant to [35 U.S.C. § 103] is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Kotzab*, 217 F.3d 1365, 1369-70 (Fed. Cir. 2000); *Merck*, 228 F. Supp.2d at 500-01. In conducting this analysis, courts have been warned not to employ "hindsight." *Kotzab*, 217 F.3d at 1369-70; *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1090-92 (Fed. Cir. 1985). In particular, "it is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992).

The evidence offered at trial demonstrates that Dr. Lenz did exactly that in forming his opinion that the asserted claims of the '122 patent are obvious. Having no education in or experience with risedronate, bisphosphonates, or the treatment of osteoporosis, Dr. Lenz went to the library to begin his work in this case. (PFF ¶ 107; Tr. at 181-82 (Lenz Cross)). At the library, Dr. Lenz reviewed various patents and publications, and conducted research on the Internet. (PFF ¶ 107; Tr. at 182-83 (Lenz Cross)). To familiarize himself with bisphosphonates in particular, Dr. Lenz reviewed the drug profiles of various bisphosphonates, including risedronate, etidronate and alendronate, in the *current version* of the Physician's Desk Reference. (PFF ¶ 108; Tr. at 182-83, 193 (Lenz Cross)). Dr. Lenz did not review drug profiles in the Physician's Desk Reference from 1984 purportedly because he

“was not able to do so” and “had no access to that” version, despite the fact that, at trial, Dr. Lenz was shown the 1984 Physician’s Desk Reference. (PFF ¶ 109; Tr. at 194 (Lenz Cross)). Had Dr. Lenz actually reviewed a Physician’s Desk Reference from 1984, he would have learned that it contained no drug profiles for risedronate, alendronate or clodronate because, as of 1984, no bisphosphonate was approved in the United States for the treatment of osteoporosis. (PFF ¶¶ 109, 161; Tr. at 195-196 (Lenz Cross); PTX I001)). In fact, the only bisphosphonate even referenced in the 1984 Physician’s Desk References was etidronate, but that compound was indicated only for Paget’s disease. (*Id.*)

Based on this evidence, it is apparent that Dr. Lenz failed to “cast[] [his] mind back to the time of invention,” *Kotzab*, 217 F.3d at 1369, and that his opinions regarding the obviousness of the ‘122 patent were not “guided only by the prior art references and the then-accepted wisdom in the field.” *Id.* Instead, Dr. Lenz improperly formed his opinions “with the claimed invention in mind.” *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 313 (Fed. Cir. 1985). As a result, Dr. Lenz’s opinion that risedronate was obvious is based on speculation and conjecture, and therefore, falls far short of meeting the standard of “clear and convincing evidence.” *See Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1290 (Fed. Cir. 2006) (“anti-hindsight jurisprudence is a test that rests on the unremarkable premise that legal determinations of obviousness, as with such determinations generally, should be based on evidence rather than on mere speculation or conjecture”).

With no reliable evidence on which to rely to support its claim of obviousness, Teva cannot meet its burden of proving that the asserted claims are invalid.

C. The ‘406 Patent Does Not Render Claims 4, 16, or 23 of the ‘122 Patent Obvious

1. The Structural Similarity of the Pyridyl EHDP Formulas Does Not Render Risedronate Obvious

At its core, Teva's obviousness argument is that 2-pyr EHDP and risedronate are structurally similar, and therefore risedronate is obvious in light of 2-pyr EHDP. Dr. Lenz opined that the "only" difference between the structure of 2-pyr EHDP and risedronate is the position of the nitrogen on the pyridine ring. (Tr. at 92:8-11 (Lenz Dir.)). Dr. Lenz's comparison of the structural similarity between these compounds is flawed because it is based on looking at two-dimensional depictions of the compounds. As courts have long recognized, a myopic focus on the structure of chemical formulas, while ignoring their chemical properties, is improper:

[A] formula is not a compound and while it may serve in a claim to identify what is being patented, as the metes and bounds of a deed identify a plot of land, the thing that is patented is not the formula but the compound identified by it. And the patentability of the thing does not depend on the similarity of its formula to that of another compound but of the similarity of the former compound to the latter. There is no basis in law for ignoring any property in making such a comparison. An assumed similarity based on a comparison of formulae must give way to evidence that the assumption is erroneous.

In re Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963).

As an initial matter, while 2-pyr EHDP and risedronate may appear similar on paper in 2-dimensional depictions, multiple structural differences exist in 3-dimensions. As a result of these 3-dimensional structural differences, the two compounds have vastly different physical, chemical and biological properties, which "could have very profound effects at different levels of pharmacological action." (PFF ¶¶ 434-35; Tr. at 594:8-11; 595:17-20 (McKenna Dir.)). Indeed, the results of P&G's efficacy and toxicity testing of the compounds in the mid-1980s demonstrated exactly that. *See infra* § III.C.4.

Consequently, the 2-dimensional structural similarity of 2-pyr EHDP and risedronate is largely irrelevant and does not render obvious the asserted claims of the '122 patent. *See*

Papesch, 315 F.2d at 391. See also *In re Fouche*, 439 F.2d 1237 (C.C.P.A. 1971) (finding positional isomers nonobvious in view of unexpected chemical properties); *In re Petrizilka*, 424 F.2d 1102 (C.C.P.A. 1970) (same); *In re Taborski*, 502 F.2d 775 (C.C.P.A. 1974) (same).

2. *It Would Not Have Been Obvious to Try Modifying 2-Pyr EHDP to Make Risedronate Because the '406 Patent Teaches Away from Pyridyl EHDP Compounds*

Teva asserts that it would have been obvious to those of ordinary skill in the art to modify the 2-pyr EHDP compound disclosed in the '406 patent to create risedronate. (Tr. at Tr. at 95:7-21 (Lenz Dir.)). However, Teva's narrow focus on just one out of the many chemical compounds disclosed in the '406 patent is improper. Courts advise that "each prior art reference must be evaluated [in its] entirety ... [then] all of the prior art must be evaluated as whole." *Panduit*, 774 F.2d at 1093-94. Each prior art reference "is relevant for all that it teaches to those of ordinary skill in the art." *Fritch*, 972 F.2d at 1264. Each reference must, therefore, be considered "not only for what it expressly teaches, but also for what it fairly suggests." *In re Bell*, 991 F.2d 781, 785 (Fed. Cir. 1993). Evaluating the '406 patent in its entirety and in the context of all of the prior art at the time, it neither teaches, nor fairly suggests, modification of the 2-pyr EHDP compound to create risedronate.

a) *The heart of the '406 patent is a dosing regimen*

The '406 patent and '122 patent are directed to the same problem, namely the impairment of bone mineralization caused by long-term use of bisphosphonates for the treatment of osteoporosis. (See PFF ¶¶ 387, 413; Tr. at 634:2-9 (McKenna Dir.); JTX 1, col. 2:5-24). More particularly, it was recognized by those skilled in the art in the mid-1980s that, at the doses necessary to treat osteoporosis, the then-existing bisphosphonates had the dual effect of inhibiting bone resorption (the desired effect) as well as inhibiting bone mineralization (the undesired effect). (PFF¶ 396; (Tr. at 375:6-24 (Bilezikian Dir.); Tr. at

609:4-9 (McKenna Dir.)). Such inhibition of bone mineralization over a long period of time could have the adverse effect of causing osteomalacia (*i.e.*, “soft bone”), which might actually increase risk of fractures. (PFF ¶¶ 166-67; Tr. at 376:1-11 (Bilezikian Dir.)).

The ‘406 patent and ‘122 patent, however, offer very different solutions to this problem. The object of the ‘122 patent is “to develop more biologically potent [bis]phosphonate compounds that can be administered at low dosage levels which cause little or no mineralization inhibition, thereby resulting in a wider margin of safety.” (JTX 1, col. 2:11-18.)

On the other hand, as Teva’s expert recognized, the “heart of the invention” of the ‘406 patent is a bisphosphonate dosing regimen “which does not result in a significant inhibition of bone formation.” (PFF ¶ 414; Tr. at 254:12-15 (Lenz Cross); JTX 5, col. 2:18-22). The ‘406 patent discloses an “on-off” regimen for administering bisphosphonates to a patient. (PFF ¶ 392; Tr. at 871:24-872:10 (Miller Dir.)). This dosing regimen includes administration of a bisphosphonate for a period of from one to ninety days, followed by a rest period of about 50 to 120 days where no bisphosphonate is administered. (PFF ¶ 392; Tr. at 608:12-18 (McKenna Dir.); JTX 5, col. 2:67–col. 3:8). In conjunction with this dosing regimen, the ‘406 patent lists no less than 36 different “examples” of compounds that may be used in the method, including 2-pyr EHDP. (JTX 5, col. 4:65 – col. 5:55).

Given that the “heart” of the ‘406 patent is a dosing regimen, that patent fairly suggests that the creation of novel bisphosphonate compounds is *not* the solution to the problem of inhibition of bone formation. (PFF ¶ 398; Tr. at 611:1-5 (McKenna Dir.)). Indeed, when evaluating the ‘406 patent in its entirety, one of ordinary skill in the art would be led to believe that the solution to the inhibition of mineralization problem was not the

development of new bisphosphonates, but rather the use of an intermittent dosing regimen with existing bisphosphonates. (*Id.*). Thus, contrary to Teva's assertion that one of skill in the art reading the '406 patent would find it obvious to try modifying 2-pyr EHDP to make risedronate, the '406 patent would instead discourage a person skilled in the art from designing novel bisphosphonate compounds, such as risedronate, to solve this problem. (PFF ¶¶ 407-08 ; Tr. at 634:2-9 (McKenna Dir.)). See also *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) ("[A] reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.").

b) The '406 patent does not suggest the selection of 2-pyr-EHDP over the numerous bisphosphonates listed

Moreover, there is nothing in the '406 patent, viewed in its entirety, that would lead a person skilled in the art to select the 2-pyridyl-EHDP compound over the numerous other bisphosphonates identified for use for in the claimed dosing regimen. (PFF ¶ 407; Tr. at 614:2-6; 614:20-23 (McKenna Dir.); JTX 5, col. 4:65–col.5:1-55). The bisphosphonates disclosed in the '406 patent are of varied structure and there is no direction given regarding which structural features are preferred or particularly advantageous. (PFF ¶¶ 404-05; Tr. at 612-614:2-16 (McKenna Dir.)). Among the list of preferred compounds that appears in the '406 patent, (JTX 5, col. 5:40-55), there is no indication that the nitrogen-containing bisphosphonates identified, including 2-pyr EHDP, are particularly preferred. (PFF ¶¶ 399, 403; Tr. at 611–612 (McKenna Dir.)). In fact, several of the preferred compounds – EHDP, Cl₂MDP and HIP – do not contain a nitrogen atom. (PFF ¶ 403; Tr. at 612:4-7 (McKenna Dir.)). Likewise, while two of the preferred compounds identified in the '406 patent have a pyridyl ring, three preferred compounds – APD, AHDP and ABDP – have a straight

hydrocarbon chain as opposed to a ring. (PFF ¶ 405; Tr. at 613:15-19 (McKenna Dir.)). In addition, there is no preference suggested in the '406 patent as to the length of the linking chain between the geminal carbon and the nitrogen. (PFF ¶ 404; Tr. at 612:20 - 6:13-11 (McKenna Dir.)).

Finally, not a single claim of the '406 patent claim is directed specifically to 2-pyr EHDP. (PFF ¶ 400; Tr. at 708:1-7 (McKenna Redir.); JTX 5, col. 17:32-col. 19:15). In contrast, there are specific claims – claims 17, 18 and 19 – that explicitly single out several of the non-pyridyl bisphosphonates. (See PFF ¶ 400; Tr. at 706:23-708:1 (McKenna Dir.); JTX 5, col. 19-20).

Therefore, in view of all this evidence, the '406 patent would not suggest selection of 2-pyr EHDP over the numerous bisphosphonates mentioned. If anything, the '406 patent would lead one of ordinary skill in the art away from pyridyl bisphosphonates such as 2-pyr EHDP to other, non-pyridyl compounds. (PFF ¶¶ 407-08; Tr. at 614:2-6 (McKenna Dir.); Tr. at 706:11-16 (McKenna Redir.); Tr. at 872:21-874:14 (Miller Dir.); JTX 5, col. 13, Table III)).

c) The '406 patent discloses lethally toxic pyridyl bisphosphonates

In addition, based on the '406 patent, one of ordinary skill in the art would be disinclined to pursue modifications of pyr-EHDP compounds because those compounds were disclosed to be lethally toxic. (PFF ¶¶ 408, 409; Tr. at 872:12 – 874:14 (Miller Dir.); JTX 5, col. 13, Table III)). In particular, the '406 patent indicates that 2-pyr EHDP is lethally toxic at the relatively low dose of 1.0 mg P/kg/day. (PFF ¶ 409; Tr. at 872:21–873:22 (Miller Dir.); JTX 5, col. 13, Table III)). According to the '406 patent, in fact, all of the pyridyl compounds tested raised toxicity concerns. (PFF ¶ 409; Tr. at 872:21-874:14 (Miller Dir.); JTX 5, col. 13, Table III)). Therefore, if anything, the '406 patent teaches away from modifying 2-pyr

EHDP and other pyridyl compounds to form risedronate, particularly given the fact that one of the objectives of researchers at that time was to identify less toxic compounds. (See PFF ¶¶ 171, 172; Tr. at 371:10-21 (Bilezikian Dir.); Tr. at 248:8-11 (Lenz Cross)). This evidence makes a finding of obviousness based on the '406 patent improper. *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000) (teaching away will overcome a showing of obviousness); *Tec Air, Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999); *Gurley*, 27 F.3d at 553.

3. “Obvious to Try” Various Positional Isomers Does Not Render Risedronate Obvious under 35 U.S.C. § 103

Even assuming Dr. Lenz were qualified to opine on what would have been obvious to one of ordinary skill in the art in the mid-1980s (which he is not), his testimony suggests, at best, that it would have been obvious to try making the 2, 3 and 4-pyr EHDP isomers. (See Tr. at 105:5-12 (Lenz Dir.)). However, “‘obvious to try’ does not equate with obviousness for purposes of Section 103.” *Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 405 F. Supp. 2d 495, 517 (D. Del. 2005); *Merck*, 228 F. Supp. 2d at 503 (citing *In re Geiger*, 815 F.2d 686, 688 (Fed. Cir. 1987) (“obvious to try various combinations does not mean that the invention was obvious.”)).

The Federal Circuit has repeatedly declared that “obvious to try” is not enough to render the claims of a patent invalid for obviousness. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) (“[T]his court and its predecessors have repeatedly emphasized that ‘obvious to try’ is not the standard under § 103.”); *N.V. Akzo v. E.I. DuPont de Nemours*, 810 F.2d 1148, 1151 (Fed. Cir. 1987) (“Of course, an ‘obvious to try’ standard is not a legitimate test of patentability.”) Rather, the proper standard under Section 103 is “whether the invention, considered as a whole, would have been obvious to one skilled in the art, not whether it would

have been obvious to one skilled in the art to try various combinations.” *N.V. Akzo*, 810 F.2d at 1151.

Accordingly, even where the patented invention may have been “obvious to try,” that invention is presumed valid unless the challenging party can demonstrate that “a skilled artisan would have perceived a reasonable expectation of success in making the invention” *Medichem*, 437 F.3d at 1165; *O’Farrell*, 853 F.2d at 904 (“For obviousness under § 103, all that is required is a reasonable expectation of success.”). To have a reasonable expectation of success in achieving the claimed invention, one of skill in the art:

must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

Medichem, 437 F.3d at 1165 (internal citations omitted). In this context, “success” is the achievement of the claimed invention, and as a consequence in this context, achievement of the intended purpose of the invention. *Id.*; *Yamanouchi Pharma. Co. v. Danbury Pharmacal Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000). *Cf. Alza* 464 F.3d at 1293 (predicate to a finding of obviousness of a chemical patent is that a person of ordinary skill in the art has a motivation to achieve the claimed invention).

Thus, to invalidate the asserted claims of the ‘122 patent, Teva was required to prove by clear and convincing evidence that, in view of the ‘406 patent, one of ordinary skill in the art would have had a reasonable expectation that risedronate would be successful as a “more biologically potent [bis]phosphonate compound[] that can be administered at low dosage levels which cause little or no mineralization inhibition, thereby resulting in a wider margin of safety.” (JTX 1, col. 2:11-18). However, the trial record is devoid of evidence demonstrating

such a reasonable expectation of success. On the contrary, the record shows that in the mid-1980s, a person of ordinary skill in the art would have had *no* expectation, let alone a reasonable one, that any particular bisphosphonate would be both safe and effective as a treatment for bone disease.

4. One of Ordinary Skill in the Art in the Mid-1980s Had No Reasonable Expectation that Risedronate would be Successful for its Intended Purpose

a) Small changes in the structure of bisphosphonates can result in significant differences in activity

As an initial matter, it is well known by those skilled in chemistry that small changes in structure can make significant differences in the chemical, biological and pharmacological properties of a particular compound. (PFF ¶ 423; Tr. at 597:14-15 (McKenna Dir.); Tr. at 203:16-21 (Lenz Cross)). P&G presented several examples of this phenomenon at trial. (See PFF ¶¶ 425-28; Tr. at 597:14-603:24 (McKenna Dir.); P-25 -- P-30, P-32). This is particularly true in the area of bisphosphonates. Researchers in the field of bisphosphonates repeatedly observed that small changes in structure could have no effect, a small effect or a large effect. (PFF ¶ 188; Tr. at 567:5-9; 567:14-18 (McKenna Dir.)).

P&G's own testing revealed numerous instances where only a slight change in the structure of a bisphosphonate produced markedly different efficacy results. (See PFF ¶¶ 231, 339-342; PTX 148). From these changes, there was no discernible pattern in terms of improving or reducing potency or in terms of the extent of the difference. (PFF ¶ 343).

b) The activity of bisphosphonates was highly unpredictable in the mid-1980s

There is no evidence suggesting that in the mid-1980s, one of ordinary skill in the art would have had any expectation that modifying the structure of 2-pyr EHDP to form risedronate would result in a compound that had an improved, or even equivalent,

safety/efficacy profile compared to 2-pyr EHDP. Nor could there be such evidence given the “embryonic” understanding of the relationship between bisphosphonate structure and bone activity at that time. (PFF ¶ 140; Tr. at 365:14-17 (Bilezikian Dir.)). While there were various bisphosphonates known in the mid-1980s, including some for treatment of bone diseases such as Paget’s disease, there was no reliable understanding of the structure-activity relationships of these bisphosphonates. (PFF ¶ 183; Tr. at 565:11-15 (McKenna Dir.)). As a result, what effect a particular structural change would have on the properties of any particular bisphosphonate could not be predicted in the mid-1980s. (PFF ¶ 187; Tr. at 597:3-7 (McKenna Dir.)).

Capturing the state of knowledge contemporaneously was Dr. Herbert Fleisch, one of the leading authorities in the field of bisphosphonates. Throughout the 1980s and early 1990s, Dr. Fleisch authored or co-authored numerous publications in which he discussed the unpredictable nature of bisphosphonates. (See PFF ¶ 191; Tr. at 567:19-579:5 (McKenna Dir.); PTX 356; PTX 355; PTX 460; PTX 461). For example, Dr. Fleisch, who is regarded as a pioneer and a founder of the study of bisphosphonates as potential drugs for bone disease, (PFF ¶ 191; Tr. at 568:3-8 (McKenna Dir.); Tr. at 382:15 – 383:9 (Bilezikian Dir.)), wrote in 1984:

It has to be emphasized that every compound, while remaining a bisphosphonate, exhibits its own physical-chemical, biological and therapeutic characteristics, so that each bisphosphonate has to be considered on its own. *To infer from one compound the effects in another is dangerous and can be misleading.*

(PFF ¶ 198; Tr. at 572:9–573:1 (McKenna Dir.); PTX 355 at 33 (emphasis added)). With respect to structure-activity relationships, Dr. Fleisch observed that “[t]he potency of inhibiting bone resorption varies widely between different bisphosphonates and *no relation has yet emerged between the structure of the bisphosphonate and its effect on bone*

resorption.” (PFF ¶ 199; Tr. at 573:12-16 (McKenna Dir.); PTX 355 at 37 (emphasis added)). In fact, even as late as 1991, according to Dr. Fleisch, “[t]he mechanism of bisphosphonate inhibition of bone resorption [was] still not clear.” (PFF ¶ 204; Tr. at 577:11-24 (McKenna Dir.); PTX 460 at 924).

The observations of Dr. Fleisch were confirmed by pharmaceutical researchers developing bisphosphonates for the treatment of osteoporosis in the mid-1980s. In particular, the inventors of U.S. Patent No. 4,621,077, which was filed in 1984 and claims alendronate (now sold by Merck as Fosamax), represented to the U.S.P.T.O. that:

one must also consider that the surprisingly high activity [of the claimed bisphosphonate] could not have been foreseen on the basis of the chemical structure insofar as it has been ably demonstrated that even small structural variations can result in substantial differences from the point of view of activity as well as tolerability of the substances.

(PFF ¶ 189; DTX 42, at col. 14:7).

P&G’s own experience with bisphosphonates confirmed this unpredictability. Although P&G wanted to be able to predict the efficacy of a particular bisphosphonate based on its structure, it found that, in order to know whether a compound was effective in inhibiting bone resorption, it had to make and test each structural variation. (PFF ¶ 228; Tr. at 425:8-426:8 (Benedict Dir.); Tr. at 530:11-20 (Benedict Cross)). Likewise, P&G determined that predicting the toxicity of various bisphosphonates was nearly impossible before testing. (PFF ¶ 228; Tr. at 428:17-429:2 (Benedict Dir.); Tr. at 529:11-20 (Benedict Cross)). Accordingly, P&G made and tested “hundreds” of bisphosphonates, “kiss[ing] a lot of frogs” along the way,⁴ because it could not predict, based on structure alone, whether a particular

⁴ To “kiss a lot of frogs,” meant that P&G had to make numerous compounds and test them in order to find the best one (PFF ¶ 242; Tr. at 436:13-437:16 (Benedict Dir.); PTX 531).

bisphosphonate would be safe and effective for the treatment of osteoporosis. (PFF ¶¶ 229, 242; Tr. at 428:5-429:2; 436:13-437:16 (Benedict Dir.); PTX 531).

The significant and unpredictable impact that a small structural change can have on the safety and efficacy of a bisphosphonate is further evidenced by P&G's testing of the 2, 3 and 4-pyr EHDP compounds. P&G's testing of risedronate yielded the unexpected result that it was significantly more potent and relatively less toxic than other bisphosphonates that it had tested, including 2-pyr EHDP. (PFF ¶ 377; Tr. at 867:10-868:20 (Miller Dir.); P-40; PTX 148 at PG78507; P-36b). Specifically, testing showed that risedronate had a safety margin ten times better than that of 2-pyr EHDP. (PFF ¶ 377; Tr. at 867:10-868:20 (Miller Dir.); PTX 148 at PG 78507; P-36b; P-40). Following these results, P&G proceeded to test the 4-pyr EHDP compound. (PFF ¶ 282; Tr. at 480:15-481:18 (Benedict Dir.); PTX 67). Those results showed that 4-pyr EHDP was "a dud" and approximately 100 times *less* potent than risedronate, further demonstrating the lack of predictability and understanding of the structure-activity relationship of bisphosphonates. (PFF ¶ 340; Tr. at 481:19-482:10 (Benedict Dir.)).

In view of this variability and unpredictability, one of ordinary skill in the art in the mid-1980s would not (and in fact could not) have had any reasonable expectation that a particular structural variation of a bisphosphonate would result in a safe and effective treatment for bone disease.

c) The mechanism of action of bisphosphonates was unknown in the 1980s

Part of the reason for the inability to predict the effect of even a small change in structure was the lack of understanding about how bisphosphonates actually work. (See PFF ¶¶ 187, 188; Tr. at 566:24-567:5 (McKenna Dir.)). In the mid-1980s, there was virtually no

understanding of how bisphosphonates worked in treating osteoporosis. (PFF ¶ 178; Tr. at 837:12-21 (Miller Dir.)). At best, researchers had speculated about possible mechanisms of action; speculation that we now know to be incorrect. (PFF ¶ 179; Tr. at 580:16-24 (McKenna Dir.)).

An understanding of how bisphosphonates work in treating bone disease such as osteoporosis is only now emerging through the use of techniques, technologies, and information that either did not exist or that researchers did not have access to in the mid-1980s. (PFF ¶ 180; Tr. at 579:22-580:15 (McKenna Dir.)). This information includes recently adduced knowledge that the mechanism of action of bisphosphonates is their interaction with and inhibition of the farnesyl pyrophosphate synthase (“FPPS”) enzyme. (PFF ¶ 442; Tr. at 582:13-24 (McKenna Dir.)). Information regarding the active site of the FPPS enzyme also is now available. (PFF ¶ 180; Tr. 580:12-15 (McKenna Dir.)). This information was gained through the use of new techniques and technologies, including the use of x-ray crystallographic studies of the interaction and complexes of the bisphosphonate with the FPPS enzyme. (PFF ¶¶ 180, 442; Tr. at 579:22-580:15, 582:13-24 (McKenna Dir.)).

In the case of nitrogen-containing bisphosphonates such as risedronate, researchers have determined that the location of the nitrogen atom is “critical” in order to achieve the right bond length and thus the right interaction between the nitrogen and the oxygen atoms at the active site on the surface of the enzyme with which it interacts. (PFF ¶ 451; Tr. at 588:20 – 589:1 (McKenna Dir.)). Moving the nitrogen atom even small distances can either make possible or abolish these interactions. (PFF ¶ 453; Tr. at 589:13-15 (McKenna Dir.)).

Knowing the mechanism of action of nitrogen-containing bisphosphonates and being able to visualize these interactions using x-ray crystallographic studies of inhibitor-enzyme

complexes, the large differences in potency among the 2, 3 and 4-pyr EHDP compounds witnessed by P&G in the mid-1980s can now be explained. (PFF ¶¶ 453-54; Tr. at 589:12-15; 591:21-24 (McKenna Dir.)). Researchers have determined that the position of the nitrogen atom in risedronate optimizes the interactions between the nitrogen and oxygen atoms at the active site, which helps to explain why risedronate is such a potent inhibitor of bone resorption. (PFF ¶ 454; Tr. at 591:21-24 (McKenna Dir.)). However, when the nitrogen is moved to the “2” or “4” position on the pyridine ring, the interactions between the nitrogen and oxygen atoms are lost or greatly weakened, thereby affecting the compound’s ability to bind in the active site, and making it much less effective as an inhibitor of bone resorption. (PFF ¶455r. at 592:5-6; Tr. at 592:1-4 (McKenna Dir.)).

Given the unpredictability of bisphosphonates and the limited understanding of how they actually worked in the mid-1980s, it is readily apparent that those of ordinary skill in the art could not have had any reasonable expectation that modification of 2-pyr EHDP to create risedronate would result in a safe and effective treatment for bone disease. *See Yamanouchi Pharma.*, 231 F3d at 1345 (no reasonable expectation of success where one of ordinary skill in art would not have reasonably expected the compound resulting from modifications to a prior art compound to have high activity, few side effects, and lacked toxicity).

d) Prior art bisphosphonates do not provide a reasonable expectation of success

Notwithstanding the recognized unpredictability of bisphosphonates and the lack of understanding of their mechanisms of action or structure-activity relationships, Dr. Lenz offered the opinion that one of ordinary skill in the art in the mid-1980s with knowledge of the prior art bisphosphonates pamidronate and alendronate would have reasonably expected that modifying 2-pyr EHDP to form risedronate would produce a compound that was safe and

effective for the treatment of bone disease. (Tr. at 107 (Lenz Dir.)). Dr. Lenz's opinion is premised on his view that the number of carbon atoms present in these various bisphosphonates would allow one of ordinary skill in the art to predict similar properties. (Tr. at 105-06 (Lenz Dir.)). However, Dr. Lenz's "carbon counting" analysis lacks merit for several reasons. (See PFF ¶ 465; Tr. at 621:12-623:2 (McKenna Dir.)).

First, as described above, there was no reliable understanding of the structure-activity relationships of bisphosphonates in the mid-1980s (*see supra* § III.C.4), and Teva offered no credible evidence that those working in the field considered the number of carbons in a compound to be a predictor of activity.

Second, while pamidronate, alendronate, 2-pyr EHDP, and risedronate are all bisphosphonates with a hydroxy substituent on the geminal carbon atom, they have numerous structural and chemical differences that affect their biological properties. (PFF ¶ 458; Tr. at 617:10-18 (McKenna Dir.)). Most notably, because of the differences in bond lengths, bond angles, and hybridization in these compounds, the carbons in the straight hydrocarbon chains of pamidronate and alendronate are different chemically from the carbons in the pyridine ring structure of 2-pyr EHDP and risedronate. (PFF ¶¶ 458-66; Tr. at 619-623 (McKenna Dir.)). As a result, one of ordinary skill in the art in the mid-1980s could not and would not have sought to predict with any reasonable expectation of success the efficacy of a bisphosphonate simply by "counting carbons." (PFF ¶ 465; Tr. at 621:12-623:2 (McKenna Dir.)).

Finally, in *Merck & Co. v. Teva Pharms. USA, Inc.*, this Court was asked to evaluate whether prior art bisphosphonates gave those of ordinary skill in the art in the mid-1980s the requisite reasonable expectation of success with respect to *alendronate*. This Court appropriately concluded that "is not possible to extrapolate the efficacy of one bisphosphonate

to another” and that “in 1982 no one could have predicted the effect that any structural changes to bisphosphonate molecules would have upon their efficacy.” *Merck*, 228 F. Supp.2d at 503; *see also Merck v. Teva Pharms. USA, Inc.*, 288 F. Supp.2d 601, 626 (D.Del. 2004) (“it was well known that each bisphosphonate had its own unique characteristics”) (overruled on other grounds).

Since the state of the art with respect to alendronate in 1982 was, for all relevant purposes, no different than it was with respect to risedronate in 1984-85, and Teva has not demonstrated otherwise, Teva’s reliance on prior art bisphosphonates to demonstrate a reasonable expectation of success is, once again, misplaced. *See Forest Labs.*, 438 F. Supp. 2d at 492 (noting that defendants had failed to demonstrate that the state of the art was different from that in a prior, related case). Quite simply, prior art bisphosphonates in the mid-1980s “fail[ed] to provide the requisite ‘reasonable expectation’ of success.” *Medichem*, 437 F.3d at 1165 (prior art does not provide reasonable expectation of success where “it teaches merely to pursue ‘a general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it’”) (citations omitted).

5. ***Objective Indicia Confirm the Validity of the ‘122 Patent***

a) *The Graham Test and Objective Indicia of Non-obviousness*

Secondary, objective indicia are “essential components of the obviousness determination” that must be considered. *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998); *Minnesota Mining & Mfg. Co. v. Johnson & Johnson Ortho., Inc.*, 976 F.2d 1559, 1573 (Fed. Cir. 1992). Trial courts may not ignore evidence of secondary considerations, including evidence of unexpected results. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). As the Federal Circuit stated in *Stratoflex, Inc. v. Aeroquip Corp.*:

[E]vidence rising out of the so-called “secondary considerations” must always when present be considered en route to a determination of obviousness. Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not.

Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530,1538 (Fed. Cir. 1983).

To infer nonobviousness, a “nexus” must be established “between the merits of the claimed invention and the evidence offered.” *Id.* at 1539; *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000).

As described in detail below, secondary, objective indicia of nonobviousness support the validity of the risedronate patent claims. Specifically, risedronate’s fulfillment of a long-felt but unsolved need in the treatment of osteoporosis, its unexpected and favorable potency and toxicity profile, as well as its commercial success all support the claims to risedronate as nonobvious. Moreover, there is a nexus between each of these secondary considerations and the asserted claims. Each of the secondary considerations relates to the properties of risedronate, and a pharmaceutical composition or method of treatment including risedronate. This is the subject matter of the asserted claims. This evidence of secondary, objective indicia thus further shows the nonobviousness of the asserted claims.

b) Long-felt, Unmet Need for a Treatment for Osteoporosis

Among the secondary considerations that must be evaluated is the existence of a long-felt but unsolved need. *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 884 (Fed. Cir. 1998). The need for a successful drug to treat osteoporosis at the time of the invention was acute. (PFF ¶¶ 140-48; Tr. at 365:14-17, 366:14-368:22, 367:11-20, 368:9-369:6, 369:16-371:21 (Bilezikian Dir.)). In the mid-1980s, osteoporosis was recognized as a serious disease. (*Id.*). Over 1.5 million osteoporotic hip fractures are sustained in the United States each year, 300,000 of which are fractures of the hip. (PFF ¶ 137; Tr. at 362:10-21

(Bilezikian Dir.)). Such hip fractures are associated with high morbidity and mortality rates. (PFF ¶ 138; Tr. at 362:22-263:13 (Bilezikian Dir.)). Twenty-five percent of individuals who sustain such hip fractures die within one year. (*Id.*).

Yet, in the mid-1980s, despite the significant toll that osteoporosis took on patients, treatments were limited to estrogen therapy and calcitonin treatment. (PFF ¶ 141; Tr. at 366:14-368:22 (Bilezikian Dir.)). Both of these treatments, however, suffered from disadvantages. (PFF ¶¶ 142-43; Tr. at 367:11-20, 368:22 (Bilezikian Dir.)). Estrogen therapy was found to cause thrombophlebitis, cardiovascular abnormalities, and increased risks of breast cancer and stroke. (PFF ¶¶ 142; Tr. at 367:11-20 (Bilezikian Dir.)). Calcitonin treatment was very expensive and required daily injections. (PFF ¶ 143; Tr. at 368:22 (Bilezikian Dir.)). The need for a successful drug to treat osteoporosis was clear, but while researchers worked diligently to address this need, it remained unmet for many years. (PFF ¶¶ 140-48; Tr. at 365:14-17, 366:14-368:22, 367:11-20, 368:9-369:6, 369:16-371:21 (Bilezikian Dir.)).

Two bisphosphonates that looked promising for the treatment of metabolic bone disorders in the mid-1980s were etidronate and clodronate. (PFF ¶ 163; Tr. at 373:4-11 (Bilezikian Dir.)). Neither of these bisphosphonates, however, was ever approved for the treatment of osteoporosis in the United States. (PFF ¶¶ 164, 170; Tr. at 338:21-23, 373:12-375:5, 377:23-378:15 (Bilezikian Dir.); Tr. at 196:1-8, 245:4-7 (Lenz Cross)). Etidronate was effective in treating Paget's disease but had much lower antiresorptive potency than risedronate. (PFF ¶ 164; Tr. at 338:21-23, 373:12-375:5 (Bilezikian Dir.)). As a result, etidronate actually inhibited the mineralization, or hardening, of bone at doses near those that would be required to inhibit resorption. (PFF ¶¶ 165-68; Tr. at 375:6-24, 376:1-24

(Bilezikian Dir.); Tr. at 423:17-424:18 (Benedict Dir.); Tr. at 609:4-9 (McKenna Dir.); Tr. at 246:8-11 (Lenz Cross)). This was an undesired side effect, which gave etidronate a poor therapeutic window that did not allow for effective treatment of osteoporosis. (*Id.*). What was needed was a compound that would inhibit bone resorption *without* inhibiting bone mineralization. (PFF ¶ 227; Tr. at 423:17-424:3 (Benedict Dir.)). Clodronate also had low antiresorptive potency and raised serious toxicity concerns, making it an unsuitable candidate drug. (PFF ¶ 170; Tr. at 377:23-378:15 (Bilezikian Dir.)). Neither clodronate nor etidronate thus satisfied the need that existed in the United States for a drug that could effectively treat osteoporosis or other metabolic bone disease.

Risedronate met this long-felt, unmet need by offering a safe and effective treatment for osteoporosis. Risedronate was found to be a significantly more potent antiresorptive agent than any of the other many compounds P&G had studied. (PFF ¶¶ 341-42; Tr. at 476:8-18, 481:19-482:10 (Benedict Dir.); Tr. at 785:22-787:4 (Eastman Dir.); PTX 148 at 78507). This was, in itself, an unexpected result that surprised even Ms. McOske, the scientist who conducted the testing. (PFF ¶¶ 314-15; Tr. at 726:11-21 (McOske Dir.); Tr. at 752:11-16 (McOske Cross)). Unlike other bisphosphonates, such as etidronate for example, risedronate does not inhibit bone mineralization (hardening) when dosed within the therapeutic range. (PFF ¶¶ 383, 485; Tr. at 380:14-381:6 (Bilezikian Dir.); Tr. at 479:4-19 (Benedict Dir.); PTX 44). In addition, risedronate had a very favorable toxicity profile. (PFF ¶¶ 354, 359; Tr. at 476:21-477:11 (Benedict Dir.); Tr. at 777:19-778:6 (Eastman Dir.); Tr. at 865:6-866:14 (Miller Dir.); PTX 82 at PG 57087). Together these properties gave risedronate the widest separation between the lowest effective dose of the compound and the highest dose at which the compound can be administered without causing toxic effects or harmful inhibition of bone

mineralization of any of the bisphosphonates tested at that time. (PFF ¶¶ 371-79; Tr. at 785:22-787:4, 792:16-795:18, 796:9-11 (Eastman Dir.); Tr. at 851:21-852:14, 867:10-868:20, 869:8-870:12 (Miller Dir.); PTX 148 at PG 78507; P-36b; P-40). Such a wide separation is most desirable for patient treatment because it provides a greater margin of safety at the consumer level and allows for more flexibility within the dosing window for different kinds of therapeutic regimens, different doses, and different clinical applications. (PFF ¶¶ 165, 372; Tr. at 423:17-424:18 (Benedict Dir.); Tr. at 852:7-14 (Miller Dir.)).

At the time of the invention claimed in the '122 patent, no other drug or treatment offered such ideal therapeutic benefits. (PFF ¶¶ 374-75; Tr. at 792:16--795:18, 796:9-11 (Eastman Dir.); PTX 148 at PG78507; P-36b). Alendronate, a different bisphosphonate that has been successful in treating osteoporosis, only became available in 1995, and ibandronate, yet another bisphosphonate used to treat osteoporosis, only entered the market within the last one-and-a-half years. (PFF ¶¶ 174-75; Tr. 379:14-20, 384:8-12 (Bilezikian Dir.)).

At the time of the invention of risedronate, the devastating and widespread impact of osteoporosis provided researchers every motivation to develop a safe and effective treatment for the disease. A solution, however, proved elusive. Risedronate was only discovered in 1985 after Dr. Benedict and other scientists all over the world had spent many years of research (since at least the mid-1970s) studying bisphosphonates in an effort to find a drug to treat osteoporosis and other metabolic bone diseases. (PFF ¶¶ 37, 162-72; Tr. at 338:21-23, 371:22-372:5, 373:4-375:24, 376:1-24, 377:1-379:7 (Bilezikian Dir.); Tr. at 414:8-24, 423:17-424:18 (Benedict Dir.); Tr. at 609:4-9 (McKenna Dir.); Tr. at Tr. at 196:1-8, 243:22-244:2, 245:4-7, 246:8-15, 248:8-249:8 (Lenz Cross); P-15; P-16). The nonobviousness of

risedronate is strongly inferred from the fact that, in spite of this long-felt need and of risedronate's ideal treatment characteristics, the drug was not discovered until 1985.

c) Unexpected Results

Other secondary considerations that must be considered are "unexpected results created by the claimed invention [and] unexpected properties of the claimed invention." *Rouffet*, 149 F.3d at 1355. Evidence of unexpected results may, for example, "consist of a comparison of test data showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have." *In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990).

Homologues, (that is, structurally related compounds), of prior art compounds are not obvious if they possess unexpected properties. *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995); *In re Chupp*, 816 F.2d 643, 644 (Fed. Cir. 1987). "[W]hen an applicant demonstrates substantially improved results . . . and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary." *Soni*, 54 F.3d at 751.

Although it was well known in the art that structure-activity relationships could not be predicted in the area of bisphosphonates. (PFF ¶¶ 182, 210, 433, 466; Tr. at (Tr. at 564:8-21, 565:11-15, 607:20-608:2, 620:6-621:11 (McKenna Dir.); Tr. at 837:22-838:6 (Miller Dir.)), the substantially superior testing results that were achieved with risedronate compared to the hundreds of others of bisphosphonates tested by P&G were unexpected and could not have been anticipated. (PFF ¶¶ 314, 316, 342, 343, 380, 383; Tr. at 476:8-18, 479:4-19, 481:19-482:10 (Benedict Dir.); 726:11-21, 727:12-17 (McOske Dir.); 870:4-871:9 (Miller Dir.); PTX 44). As discussed *supra*, risedronate was found to be appreciably more potent as an antiresorptive agent than any other compound P&G studied. (PFF ¶¶ 342, 377; Tr. at 476:8-

18, 481:19-482:10 (Benedict Dir.); PTX 148; P-036b) In addition, risedronate had a very favorable toxicity profile. (PFF ¶¶ 354, 359; Tr. at 476:21-477:11 (Benedict Dir.), 777:19-778:6 (Eastman Dir.); Tr. at 865:6-866:14 (Miller Dir.); PTX 82 at PG 57087) Risedronate was also found not to inhibit bone mineralization (hardening) when dosed within the therapeutic range. As a result, risedronate unexpectedly exhibited a safety to efficacy ratio (or therapeutic index) in its compound-screening program that was at least *ten times* better than any of the other compounds tested. (Tr. at 867:10-868:20 (Miller Dir.); P-40; PTX 148 at PG 78507; P-36b)

In particular, risedronate possesses unexpected results when compared to the structurally similar positional isomer, 2-pyr EHDP. 2-pyr EHDP was synthesized and tested before risedronate (3-pyr EHDP). (PFF ¶¶ 264, 274; Tr. at 420:19-421:1, 457:14-22, 467:5-22 (Benedict Dir.); PTX 67 at PG 53521-53522) Nevertheless, the antiresorptive activity of risedronate, once tested, was more than three times that of 2-pyr EHDP, and the toxicity profile (no observed effects level, or NOEL) of risedronate was three times superior to that of 2-pyr EHDP. (PFF ¶¶ 337, 339, 342; Tr. at 476:8-18, 481:19-482:10 (Benedict Dir.), 859:11-864:9 (Miller Dir.); P-39). These results and the underlying properties of the compound that give rise to them could not have been predicted or anticipated either based on the 2-pyr EHDP compound or any other compound and were thus completely unexpected. In fact, it was risedronate's unexpected substantial superiority to all other compounds tested – as measured by the ratio of safety to efficacy – that led P&G to make risedronate its lead compound for development and, upon further study and FDA approval, the commercially successful drug today known as Actonel. (PFF ¶ 379, 385; Tr. at 482:11-483:4 (Benedict Dir.), 869:14-870:12 (Miller Dir.); PTX 148 at PG 78507; P-36b).

The nonobviousness of risedronate is thus demonstrated by the completely unexpected desirable properties that the compound exhibits. Had the favorable properties of such a compound been obvious to one of skill in the art, particularly in light of the long-felt need for a compound possessing such particular attributes, then the compound would have been explored and discovered long before Dr. Benedict did so in 1985.

There is a nexus between these unexpected results and the asserted claims. The asserted claims are all specifically directed to risedronate and its use in a pharmaceutical composition and method of treatment, and the unexpected results are based upon risedronate's inherent properties. Such unexpected properties of risedronate cannot be ignored in judging the validity of the asserted claims. *Minnesota Mining*, 976 F.2d at 1573 ("unexpected results must be considered before a conclusion on obviousness is reached."); *In re Lunsford*, 327 F.2d 526, 528 (C.C.P.A. 1964) (an "unobvious property inherent in the claimed compounds" found sufficient to overcome a showing of very close structural obviousness); *In re Ward*, 329 F.2d 1021, 1023 (C.C.P.A. 1964).

d) Commercial Success of the Invention

"The commercial response to an invention is significant in determinations of obviousness, and is entitled to fair weight." *Demaco Corp. v. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988); *Forest Labs.*, 438 F. Supp.2d at 494 (citing same). A patentee makes a *prima facie* showing of commercial success by demonstrating "significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent." *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997); *Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000). Once this showing is made, "it is presumed that the commercial success is due to the patented invention." *J.T. Eaton*, 106 F.3d at 1571. Thereafter, the burden shifts to the

defendant to prove that the commercial success was instead due to factors other than the patented invention. *See Ecolochem*, 227 F.3d at 1377.

Here, the record reflects, and Teva does not dispute, that Actonel is an “unequivocal commercial success.” (PFF ¶ 505; Tr. at 961:16-962:6, 993:12-20 (Smith Dir)).⁵ Since Actonel was launched for the treatment of osteoporosis in April 2000, (Joint Statement, ¶ 15), Actonel has achieved the status of a “blockbuster drug,” *i.e.*, a drug with sales of a billion dollars or more annually. (PFF ¶ 498; Tr. at 962:13-24 (Smith Dir.)). To date, Actonel has generated sales of more than \$2.7 billion, (*see* DTX 124,) and has consistently outpaced internal estimates developed for P&G prior to launch. (PFF ¶¶ 497, 503 Tr. at 962:9-12, 965:16-967:4 (Smith Dir.); DTX 124; P-41). Significantly, Actonel achieved blockbuster status despite late entry into a market for osteoporosis treatments with two or three significant competitors, including Merck’s Fosamax, which had been on the market for five years, (PFF ¶ 496; Tr. at 964:23-965:15, 970:2-8 (Smith Dir.)). Actonel also achieved blockbuster status despite P&G spending less on marketing than that of its more established competitors. (PFF ¶ 512; Tr. at 978:3-980:8 (Smith Dir.); DTX 132 at PGK13663-64). Despite these competitive hurdles, since launch in April 2000, Actonel’s market share grew steadily from 2.8% in 2000, to 8.1% in 2001, to 12.5% in 2002, to 18.8% in 2003, to 25% in 2004, and over 25% in 2005. (PFF ¶ 501; Tr. at 967:5-968:11 (Smith Dir.); P-43). This constant market share gain came at the expense of Actonel’s more entrenched competitors, such as Fosamax and Eli Lilly’s Evista. (PFF ¶ 501; Tr. at 968:12-969:17 (Smith Dir.)).

In addition, the record evidence demonstrates that Actonel’s commercial success was due to the claimed benefits of the ‘122 patent. (PFF ¶ 507; Tr. at 970:18-971:7 (Smith Dir.)). As Dr. Smith explained, in the pharmaceutical industry, drugs that are late entrants to the

⁵ Teva’s expert on economics, Dr. Jesse David, did does dispute that Actonel is a commercial success.

market can achieve “blockbuster” status if they are unique in an important attribute, such as efficacy or favorable side effect profile. (PFF ¶ 513; Tr. at 972:15-973:6 (Smith Dir.); PTX 323). In the case of Actonel, market research reports demonstrate that, based on their prescribing behavior, doctors believe that Actonel delivers the same or comparable efficacy as existing products, (primarily Fosamax,) but with a noticeably better side effect profile, particularly with respect to gastrointestinal tolerability. (PFF ¶ 514; Tr. at 385:3-386:9 (Bilezikian Dir.); Tr. at 973:21-975:10 (Smith Dir.)).

In other words, physicians believe, based on their own experience, as well as experiential data from their colleagues, that Actonel has a better therapeutic index than other existing products, which was a primary objective of the invention of the ‘122 patent. (PFF ¶ 514; PTX 322; JTX 1).

Indeed, surveys indicate that physicians have a higher overall level of satisfaction with Actonel as compared to its primary competitor, Fosamax. (PFF ¶ 515; Tr. at 987:21-990:18 (Smith Dir.); PTX 523 at PG80467). Prescription data supports this observation, showing that prescription refills for Actonel have been steady, and by 2005, represented about 70% of Actonel’s sales. (PFF ¶ 515; Tr. at 984:9-987:20 (Smith Dir.); PTX 319; PTX 320; PTX 321; P-42). Because, as Dr. Smith explained, repeat prescriptions are independent of any marketing, they are particularly compelling evidence that Actonel’s success is due to its inherent benefits. (*Id.*)

e) The Testimony of Teva’s “Economic Expert” is Inadmissible

In an effort to challenge the commercial success of Actonel and its connection to the ‘122 patent, Teva offered the testimony of an economist, Dr. Jesse David. However, Dr. David did not actually dispute that Actonel is a commercial success. (PFF ¶ 518; Tr. at 301:15-21 (David Cross)). Nor did Dr. David dispute that there is a nexus between the

claimed benefits of the '122 patent and the commercial success of Actonel. (PFF ¶ 519; Tr. at 301:02 (David Cross)). Instead, Dr. David testified that he had "addressed the relevance of commercial success" in this case, (PFF ¶ 523; Tr. at 301:12-13 (David Cross)), and that in his opinion, the commercial success of Actonel is not relevant to the non-obviousness of the '122 patent. (Tr. at 298:14-19 (David Dir.)).

Dr. David's opinion regarding the evidentiary weight that should be accorded evidence of commercial success is an inadmissible legal conclusion that can in no way "assist the trier of fact to understand the evidence or to determine a fact in issue." Fed. R. Evid. 702. As such, Dr. David's opinion is not the proper subject of expert testimony, and therefore should be precluded. *See, e.g., Watkins v. New Castle County*, 374 F. Supp. 2d 379, 392-93 (D. Del. 2005) (precluding testimony of an expert witness as to whether defendants' conduct satisfied the legal standard at issue); *Lynch v. J.P. Stevens & Co., Inc.*, 758 F.Supp. 976, 1014 (D.N.J. 1991) ("Legal conclusions are not within the ambit of expert testimony permitted under Rule 703."); *see also, e.g., Williams v. Wal-Mart*, 922 F.2d 1357, 1360 (8th Cir.1990) (court may exclude expert testimony if it is nothing more than legal conclusions).

Even if Dr. David's opinion were admissible, however, it would be irrelevant. As Dr. David acknowledged, his opinion regarding the "relevance of commercial success" was dependent upon the assumption that the '406 patent, and specifically the 2-pyr EHDP compound, was relevant prior art at the time risedronate was invented. (PFF ¶ 525; Tr. at 298:23-24 (David Dir.); Tr. at 324:22-325:11; 327:20-328:3 (David Cross)). As discussed *supra* at § II, 2-pyr EHDP was not prior art to risedronate. As such, Dr. David, as he readily admitted at trial, has no opinion applicable to the facts of this case. (PFF ¶ 527; Tr. at 325:17-21 (David Cross)).

IV. THE '122 PATENT IS NOT INVALID FOR OBVIOUS-TYPE DOUBLE PATENTING

In apparent recognition that its arguments inevitably fail under 35 U.S.C. § 103, at trial Teva turned to the judicially created doctrine of obviousness-type double patenting to support its attack on the invalidity of the '122 patent. Teva argued that the asserted claims of the '122 patent were invalid for obviousness-type double patenting in view of claim 15 of the '406 patent. Once again, however, Teva's arguments are unsupported by both the law and the evidence. In particular, because the questions Teva raised as to the validity of the '122 patent "on the ground of section 103 obviousness lack merit, the Court need not engage in a redundant double-patenting inquiry." *Sanofi v. Apotex, Inc.*, No. 02 Civ. 2255 (SHS), 2006 WL 2516486, *18 (S.D.N.Y. Aug. 31, 2006).

The judicial doctrine of obviousness-type double patenting prevents a patent claim from validly issuing when it "is obvious over, or anticipated by" a claim in an earlier patent. *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001). In general, the "same type of analysis is used for an obviousness-type double patenting inquiry as for a § 103 obviousness inquiry." *Affymetrix, Inc. v. PE Corp.*, 01 Civ. 0634, 2002 U.S. Dist. LEXIS 24649, at *5 n. 3 (S.D.N.Y. Dec 24, 2002); *Ortho Pharma. Corp. v. Smith*, 959 F.2d 936, 943 (Fed. Cir. 1992); *see also In re Baird*, 348 F.2d 974, 979 (C.C.P.A. 1965) ("This [double-patenting] problem may also be stated to be whether it would have been obvious to one of ordinary skill to modify the process of the patent claims."). However, the test for obviousness-type double patenting is narrower than the statutory obviousness inquiry pursuant to 35 U.S.C. § 103. *See Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1378 (Fed. Cir. 2003). "Obviousness compares claimed subject matter to the prior art;

nonstatutory double patenting compares claims in an earlier patent to claims in a later patent or application.” *Geneva Pharm.*, 349 F.3d at 1378.

Teva challenges the validity of the ‘122 patent on the basis of non-statutory double patenting, and therefore bears the burden of establishing invalidity by clear and convincing evidence. *See Pfizer*, 405 F. Supp 2d at 513. This burden of proof is “heavy and unshifting.” *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1580 (Fed. Cir. 1991). To prove that the asserted claims of the ‘122 patent are invalid for obviousness-type double patenting in view of claim 15 of the ‘406 patent, Teva was required to prove by clear and convincing evidence that the asserted claims would have been obvious to one of ordinary skill in the art in the mid-1980s based upon the teachings of that claim. *See* MPEP § 804(II)(B)(1); *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 364 F. Supp. 2d 820, 911 (S.D. Ind. 2005) (obviousness-type double patenting mirrors obviousness analysis under *Graham v. John Deere Co.*, 383 U.S. 1 (1966)); *cf. In re Emert*, 124 F.3d 1458, 1462 (Fed. Cir. 1997) (“Absent some indication of unexpected properties, the [patented] combination rendered [the claimed invention] obvious [for double patenting].”).

As an initial matter, Teva’s obviousness-type double patenting argument is premised on a fundamental misapplication of the law. At trial, Teva intentionally focused the Court on the disclosure of a single compound—2-pyr EHDP—while conspicuously ignoring the actual claims of the ‘406 patent as a whole. (*See* Tr. 15:13 – 16:15 (Teva Opening)). Double patenting is, however, “determined by analysis of the claims *as a whole*.” *Carman Indus., Inc. v. Wahl*, 724 F.2d 932, 940 (Fed. Cir. 1983) (emphasis added); *General Foods Corp. v. Studiengesellschaft Kohle*, 972 F.2d 1272, 1274-1275 (Fed. Cir. 1992) (“patent claims, being

definitions which must be read *as a whole*, do not ‘claim’ or cover or protect all that their words may disclose.”) (emphasis in original).

Here, Teva failed to prove at trial that the ‘122 patent was obvious in light of the ‘406 patent as a whole, and, as a result, also failed to prove that the asserted claims of the ‘122 patent were obvious under the narrower standard of obviousness-type double patenting, that is, in light of only the claims of the ‘406 patent. *See Sanofi*, 2006 WL 2516486 at *18. As demonstrated at trial, all of the claims of the ‘406 patent are directed to a dosing regimen, and, in particular, claim 15 lists eight “examples” of compounds that may be used in the regimen, only one of which is 2-pyr EHDP. (PFF ¶¶ 418-19; Tr. at 629:16-633:13 (McKenna Dir.); JTX 5, col. 2:67- col.5:55). This dosing regimen is a patentably distinct invention from the asserted claims of the ‘122 patent. Claims 4, 16 and 23 of the ‘122 patent are unrelated to any particular dosing regimen and instead relate to a novel bisphosphonate compound, a pharmaceutical composition comprising that compound, and a method of use for that compound. Therefore, Teva’s selective focus on only one compound described as an example in a claimed dosing regimen is improper.

Moreover, for all the reasons described above, risedronate would not be obvious to a person of ordinary skill in the art in the mid-1980s comparing only claim 15 (or any claim) of the ‘406 patent to the asserted claims of the ‘122 patent. (*See supra* § IV). Risedronate does not appear in any claim of the ‘406 patent. As discussed *supra*, not one of the ‘406 patent claims is directed generally to 2-pyr EHDP as a novel compound or its use for the treatment of bone disease. (See JTX 5, col. 17:32 – col. 20:15). Instead, the claims of the ‘406 patent are directed to an “on-off” dosing regimen that teaches away from the use of novel, pyridyl bisphosphonates to treat bone disease. (*See supra* §III.C.2.a). In addition, the

unpredictability and lack of understanding of the structure-activity relationship of bisphosphonates provides no reasonable expectation that modifying 2-pyr EHDP to create risedronate would be successful in producing a compound useful for its intended purpose. (*See supra* § III.C.4).

As a result, Teva does not satisfy its heavy burden of demonstrating obviousness-type double patenting by clear and convincing evidence. *See Pfizer*, 405 F. Supp.2d at 516 (“Because the Court has concluded that distinct differences exist between claims [of the patents] rendering them patentably distinct, the Court concludes that [the defendant] has not established invalidity ... on the grounds of non-statutory double patenting.”).

V. PROPOSED CONCLUSIONS OF LAW

Based on all of the evidence in the record, P&G’s Proposed Findings of Fact, and the foregoing content of P&G’s Post-Trial Brief, P&G respectfully submits the following proposed Conclusions of Law:

1. Obviousness is to be determined “at the time the invention was made.” 35 U.S.C. § 103; *Graham v. John Deere Co.*, 383 U.S. 1 at 14-15 (1966). Pertinent prior art, therefore, only includes those references with effective dates prior to the date of the invention. *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1453 (Fed. Cir. 1984). Priority therefore involves two components: (1) conception and (2) reasonable diligence in later reducing the invention to practice. *LifeScan, Inc. v. Home Diagnostics, Inc.*, 103 F. Supp. 2d 345, 367 (D. Del. 2000).

2. Conception of a chemical compound requires the structure of the chemical compound, and possession of an operative method of making it. *Oka v. Youssefyeh*, 849 F.2d 581, 583 (Fed. Cir. 1988); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991).

3. Although courts require corroboration of an inventor's testimony as to conception, *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994), a rule of reason applies to the corroboration requirement. *Price v. Symsek*, 988 F.2d 1187, 1195 (Fed. Cir. 1993). Contemporaneous lab notebooks provide sufficient corroboration. *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1169-70 (Fed. Cir. 2006); *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1577-78 (Fed. Cir. 1996).

4. "An actual reduction to practice occurs when the inventor (1) constructs a product or performs a process that is within the scope of the claimed invention; and (2) demonstrates that the invention actually worked for its intended purpose." *LifeScan*, 103 F. Supp. 2d at 367; *Cooper v. Goldfarb*, 154 F.3d 1321, 1327 (Fed. Cir. 1998); *Estee Lauder Inc. v. L'Oreal S.A.*, 129 F.3d 588, 593 (Fed. Cir. 1997); *Kimberly-Clark*, 745 F.2d at 1445.

5. If a patent's claims to a pharmaceutical compound contain no limitation relating to intended use or to discovered properties, "practical utility may be shown by adequate evidence of any pharmaceutical activity." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564 (Fed. Cir. 1996). For test results to satisfy the practical utility requirement, "there must be a sufficient correlation between the tests and an asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa*, 93 F.3d at 1564. However, the "test results need not absolutely prove that the compound is pharmacologically active." *Id.* "[T]he mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." Manual of Patent Examining Procedure ("MPEP") § 2107.01 at 2100-25. Data from human clinical trials are not required to show utility. MPEP § 2107.03 at

2100-35. Moreover, “proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility.” *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995).

6. The filing of a patent application that describes and enables the claimed invention is a “constructive reduction to practice of the invention.” *Chen v. Bouchard*, 347 F.3d 1299, 1305 (Fed. Cir. 2003).

7. Corroboration of an inventor’s testimony is required to establish actual reduction to practice. *Medichem*, 437 F.3d at 1169. Unlike inventors’ oral testimony, the condition of “corroboration” is not imposed on a lab notebook or other documentary or physical evidence as a condition to that item serving as evidence of reduction to practice. *Medichem*, 437 F.3d at 1169-70; *Mahurkar*, 79 F.3d at 1577-78. Although an unwitnessed notebook is not sufficient standing alone to support a claim of reduction to practice, “a notebook, unlike the oral testimony of an inventor, may be weighed, for whatever it is worth, in the final determination of reduction to practice.” *Medichem*, 437 F.3d at 1170; *Hahn v. Wong*, 892 F.2d 1028, 1033 (Fed. Cir. 1989); *Reese v. Hurst*, 661 F.2d 1222, 1232 (C.C.P.A. 1981). “Independent corroboration may consist of testimony of a witness, other than the inventor, to the actual reduction to practice or it may consist of evidence of surrounding facts and circumstances independent of information received from the inventor.” *Reese*, 661 F.2d at 1225. “The law does not impose an impossible standard of ‘independence’ on corroborative evidence by requiring that every point of a reduction to practice be corroborated by evidence having a source totally independent of the inventor.” *Cooper*, 154 F.3d at 1330.

8. When a patented invention is conceived prior to the filing date of a reference asserted as prior art, but reduced to practice after the filing date of that reference, the party

challenging the validity of the patent must prove by clear and convincing evidence that the alleged prior art patent was filed before the effective invention date for the challenged patent. *Mahurkar*, 79 F.3d at 1578; *see also Loral Fairchild Corp. v. Matsushita Elec. Indus. Co.*, 266 F.3d 1358, 1362-63 (Fed. Cir. 2001).

9. To demonstrate reasonable diligence, it is not necessary for a party alleging prior invention to have dropped all other work and concentrated solely on the particular invention involved. *Rines v. Morgan*, 250 F.2d 365, 369 (C.C.P.A. 1957); *Izumi Prods. Co. v. Koninklijke Philips Elecs. N.V.*, 315 F. Supp. 2d 589, 608 (D. Del. 2004). There also need not be evidence of activity on every single day if a satisfactory explanation is evidenced. *Monsanto Co. v. Mycogen Plant Sci., Inc.*, 261 F.3d 1356, 1369 (Fed. Cir. 2002); *Izumi Prods.*, 315 F. Supp. 2d at 608. Additionally, determining whether the required “reasonable diligence” has been satisfied involves specific inquiry. *Monsanto*, 261 F.3d at 1369; *Izumi Prods.*, 315 F. Supp. 2d at 608.

10. Dr. Benedict conceived the inventions of claims 4, 16, and 23 of the ‘122 patent before the filing of the ‘406 patent application and was diligent in reducing those inventions to practice thereafter.

11. The ‘406 patent is not prior art to claims 4, 16, and 23 of the ‘122 patent.

12. The ‘122 patent is presumed valid. *See* 35 U.S.C. § 282. This presumption extends to each independent and dependent claim of the patent, irrespective of the validity of the other claims. *Bausch & Lomb, Inc. v. Barnes Hind/Hydrocurve, Inc.*, 796 F.2d 443, 446-47 (Fed. Cir. 1986).

13. To overcome this presumption, Teva must demonstrate by clear and convincing evidence that the ‘122 patent is invalid. *Boehringer Ingelheim Vetmedica, Inc. v. Schering-*

Plough Corp., 320 F.3d 1339, 1353 (Fed. Cir. 2003); *Forest Labs. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 485 (Farnan, J.). “Clear and convincing” evidence is evidence that “proves in the mind of the trier of fact an abiding conviction that the truth of a factual contention is highly probable.” *Intel Corp. v. International Trade Comm’n*, 946 F.2d 821, 830 (Fed. Cir. 1991); *see also Merck & Co. v. Teva Pharms. USA, Inc.*, 228 F. Supp. 2d 480, 496 (D. Del. 2002).

14. Obviousness is a legal determination, which turns on the objective analysis of underlying factual inquiries. *Forest Labs.*, 438 F.Supp.2d at 492. Specifically, the trier of fact must consider four issues: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness. *Id.* (citing *Graham*, 383 U.S. at 17-18).

15. The obviousness of a patented invention is determined from the perspective of one of ordinary skill in the art, *In re Gorham*, 933 F.2d 982, 986 (Fed. Cir. 1991), and the law presumes that the hypothetical person of ordinary skill knows all relevant prior art. *See Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985).

16. Factors that may be used in determining the level of ordinary skill in the art, include: (1) the educational level of the inventor; (2) the types of problems encountered in the art; (3) the prior art solutions to those problems; (4) the rapidity with which innovations are made; (5) the sophistication of the technology; and (6) the educational level of active workers in the field. *See e.g., Envtl. Designs Ltd. v. Union Oil Co. of Calif.*, 713 F.2d 693, 696 (Fed. Cir. 1983). “These factors need not be present in every case and certain factors may be more

predominate in some cases than in others.” *Forest Labs.*, 438 F. Supp.2d at 488 (citing *Envtl. Designs*, 713 F.2d at 696-97).

17. To qualify as an expert under Federal Rule of Evidence 702, a witness must first establish his expertise by demonstrating “knowledge, skill, experience, training, or education” in the relevant subject area. *See* Fed. R. Evid. 702.

18. Teva’s technical expert, Dr. George Lenz, is not qualified to offer opinions on what persons of ordinary skill in the art relevant to the field of the ‘122 patent would have known or believed in the mid-1980s.

19. Teva has offered no admissible evidence that the ‘122 patent was obvious in view of the relevant prior art.

20. Teva’s analysis of the validity of the ‘122 patent and the asserted prior art is based entirely on impermissible hindsight analysis. *See In re Kotzab*, 217 F.3d 1365, 1369-70 (Fed. Cir. 2000); *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992); *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1090-92 (Fed. Cir. 1985); *Merck*, 228 F. Supp. 2d at 500-01.

21. In analyzing the patentability of a claim to a chemical compound, it is improper to focus on the structure of chemical formulas, while ignoring their chemical properties. *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963).

22. In assessing obviousness, “each prior art reference must be evaluated [in its] entirety ... [then] all of the prior art must be evaluated as whole.” *Panduit*, 774 F.2d at 1093-94. Each prior art reference “is relevant for all that it teaches to those of ordinary skill in the art.” *In re Fritch*, 972 F.2d 1260, 1264 (Fed. Cir. 1992). Each reference must, therefore, be considered “not only for what it expressly teaches, but also for what it fairly suggests.” *In re Bell*, 991 F.2d 781, 785 (Fed. Cir. 1993).

23. A reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. *Winner Intern. Royalty Corp. v. Wang*, 202 F.3d 1340, 1350 (Fed. Cir. 2000); *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

24. In order to demonstrate that an invention is obvious for purposes of Section 103, it is not sufficient to demonstrate that it would have been obvious to try various combinations. *Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 405 F. Supp. 2d 495, 517 (D. Del. 2005); *Merck*, 228 F. Supp.2d at 503. *See also In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); *N.V. Akzo v. E.I. DuPont de Nemours*, 810 F.2d 1148, 1151 (Fed. Cir. 1987).

25. Rather, the proper standard under Section 103 is "whether the invention, considered as a whole, would have been obvious to one skilled in the art, not whether it would have been obvious to one skilled in the art to try various combinations." *N.V. Akzo*, 810 F.2d at 1151.

26. Even where the patented invention may have been "obvious to try," that invention is presumed valid unless the challenging party can demonstrate that "a skilled artisan would have perceived a reasonable expectation of success in making the invention" *Medichem*, 437 F.3d at 1165.

27. To have a reasonable expectation of success in achieving the claimed invention, one of skill in the art "must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Medichem*, 437 F.3d at 1165. In this context, "success" is the achievement of the intended purpose of the invention. *See id.*;

Yamanouchi Pharma. Co. v. Danbury Pharmacal Inc., 231 F.3d 1339, 1345 (Fed. Cir. 2000).

Cf. Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1293 (Fed. Cir. 2006).

28. The '406 patent teaches away from the inventions of claims 4, 16, and 23 of the '122 patent.

29. It would not have been obvious to one of skill in the art in the mid-1980s to select 2-pyr EHDP from among the compounds identified in the '406 patent and to try modifying it to form risedronate, with a reasonable expectation that such modifications would result in a compound that was safe and effective for treating diseases associated with abnormal calcium and phosphate metabolism.

30. Secondary, objective indicia are “essential components of the obviousness determination” that must be considered. *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998); *Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1573 (Fed. Cir. 1992). Trial courts may not ignore evidence of secondary considerations. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

31. To infer nonobviousness based upon secondary considerations, a “nexus” must be established “between the merits of the claimed invention and the evidence offered.” *Stratoflex*, 713 F.2d at 1539; *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000).

32. Among the secondary considerations that must be evaluated is the existence of a long-felt but unsolved need. *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 884 (Fed. Cir. 1998).

33. The existence of a long-felt but unsolved need for a safe and effective treatment for osteoporosis supports the non-obviousness of claims 4, 16, and 23 of the '122 patent.

34. Other secondary considerations that must be considered are "unexpected results created by the claimed invention and unexpected properties of the claimed invention." *Rouffet*, 149 F.3d at 1355. Evidence of unexpected results may "consist of a comparison of test data showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have." *In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990); *Soni*, 54 F.3d at 751; *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987). "When an applicant demonstrates substantially improved results . . . and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary." *Soni*, 54 F.3d at 751.

35. The unexpectedly improved safety and efficacy properties of risedronate (as compared to prior art compounds) supports the non-obviousness of claims 4, 16, and 23 of the '122 patent.

36. "The commercial response to an invention is significant in determinations of obviousness, and is entitled to fair weight." *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988); *Forest Labs.*, 438 F. Supp.2d at 494. A patentee makes a *prima facie* showing of commercial success by demonstrating "significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent." *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997); *Ecolchem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000). Once this showing is made, "it is presumed that the commercial success is due to the patented invention." *J.T. Eaton*, 106 F.3d at 1571. Thereafter, the burden shifts to the defendant to

prove that the commercial success was instead due to factors other than the patented invention. *See Ecolchem*, 227 F.3d at 1377.

37. P&G has made a *prima facie* showing of the commercial success of Actonel, creating a presumption that such success is due to the patented invention. Teva has not met its burden of proving that the commercial success of Actonel is due to factors other than the patented invention.

38. Dr. David's opinion regarding the evidentiary weight that should be accorded evidence of commercial success is an inadmissible legal conclusion and is not the proper subject of expert testimony. *See* Fed. R. Evid. 702; *Watkins v. New Castle County*, 374 F. Supp. 2d 379, 392-93 (D. Del. 2005); *Lynch v. J.P. Stevens & Co., Inc.*, 758 F. Supp. 976, 1014 (D.N.J. 1991); *see also, e.g., Williams v. Wal-Mart Stores, Inc.*, 922 F.2d 1357, 1360 (8th Cir. 1990).

39. The '122 patent is not obvious in view of the '406 patent.

40. The judicial doctrine of obviousness-type double patenting prevents a patent claim from validly issuing when it "is obvious over, or anticipated by" a claim in an earlier patent. *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001). In general, the "same type of analysis is used for an obviousness-type double patenting inquiry as for a § 103 obviousness inquiry." *Affymetrix, Inc. v. PE Corp.*, No. 01 Civ. 0634, 2002 U.S. Dist. LEXIS 24649, at *5 n. 3 (S.D.N.Y. Dec 24, 2002); *Ortho Pharmaceutical Corp. v. Smith*, 959 F.2d 936, 940 (Fed. Cir. 1992); *see also In re Baird*, 348 F.2d 974, 979 (C.C.P.A. 1965).

41. The test for obviousness-type double patenting is narrower than the statutory obviousness inquiry pursuant to 35 U.S.C. § 103. *See Geneva Pharm., Inc. v. Glaxosmithkline PLC*, 349 F.3d 1373, 1378 (Fed. Cir. 2003); *In re Jezl*, 396 F.2d 1009, 1013

(C.C.P.A. 1968). “Obviousness compares claimed subject matter to the prior art; nonstatutory double patenting compares claims in an earlier patent to claims in a later patent or application.” *Geneva Pharm.*, 349 F.3d at 1378.

42. Teva bears the burden of establishing invalidity based on obviousness-type double patenting by clear and convincing evidence. *See Pfizer*, 405 F. Supp. 2d at, 513. This burden of proof is “heavy and unshifting.” *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1580 (Fed. Cir. 1991).

43. To prove that the asserted claims of the ‘122 patent are invalid for obviousness-type double patenting in view of claim 15 of the ‘406 patent, Teva was required to prove by clear and convincing evidence that the asserted claims would have been obvious to one of ordinary skill in the art in the mid-1980s based upon the teachings of that claim. *See* MPEP § 804(II)(B)(1); *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 364 F. Supp. 2d 820, 911 (S.D. Ind. 2005). *Cf. In re Emert*, 124 F.3d 1458, 1462 (Fed. Cir. 1997).

44. Double patenting is “determined by analysis of the claims as a whole.” *Carman Indus., Inc. v. Wahl*, 724 F.2d 932, 940 (Fed. Cir. 1983); *General Foods Corp. v. Studiengesellschaft Kohle*, 972 F.2d 1272, 1274-1275 (Fed. Cir. 1992).

45. Because Teva failed to demonstrate that the asserted claims of the ‘122 patent were obvious under 35 U.S.C. § 103, it also cannot meet its burden of proving obviousness-type double patenting. *See Sanofi v. Apotex, Inc.*, No. 02 Civ. 2255 (SHS), 2006 WL 2516486, *18 (S.D.N.Y. Aug. 31, 2006).

46. Claims 4, 16, and 23 of the ‘122 patent are not rendered invalid due to obviousness-type double patenting in view of claim 15 of the ‘406 patent.

47. Claims 4, 16, and 23 of the '122 patent are not rendered invalid due to obviousness-type double patenting in view of any claim of the '406 patent.

48. Claims 4, 16, and 23 of the '122 patent are valid.

49. Claims 4, 16, and 23 of the '122 patent are infringed by Teva.


VI. CONCLUSION

WHEREFORE, for all the foregoing reasons, Procter & Gamble prays that this Court grant the following relief:

- (a) A declaration that the '122 Patent is valid and enforceable;
- (b) A judgment that a claim or claims of the '122 Patent are infringed by the Teva ANDA Risedronate Tablets, that Teva's submission of its ANDA No. 77-132 is an act of infringement, and that Teva's making, using, offering to sell, selling, or importing the Teva ANDA Risedronate Tablets will infringe the '122 Patent;
- (c) An Order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any approval of Teva's ANDA No. 77-132 shall be a date which is not earlier than the expiration date of the '122 Patent;
- (d) An Order permanently enjoining Teva, and its affiliates and subsidiaries, and each of their officers, agents, servants and employees, from making, using, offering to sell, selling, or importing the Teva ANDA Risedronate Tablets until after the expiration date of the '122 Patent;
- (e) Reasonable costs of suit incurred by Procter & Gamble in this action; and
- (f) Such further and other relief as this Court deems proper and just.

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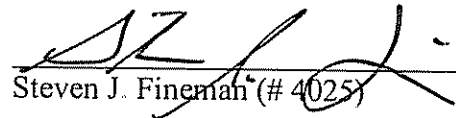
CERTIFICATE OF SERVICE

I hereby certify that on December 20, 2006, I electronically filed the foregoing document with the Clerk of the Court using CM/ECF which will send notification of such filing(s) and Hand Delivered to the following:

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